46th Annual Meeting of the Swiss Society of Nephrology (SGN-SSN)

Interlaken (Switzerland), December 4–5, 2014
A Registry of Patients with Autosomal Dominant 
Tubulointerstitial Kidney Diseases (NCCR project)
Eric Olinger1, Karin Daham2, Olivier Bonny3, Olivier Devuyst1
1Institute of Pathology and Genetics, Gosselies, Belgium; 2Dépt. de Pharmacologie et de Toxicologie, Service de Néphrologie, CHUV, Lausanne

Background: Autosomal dominant tubulointerstitial kidney diseases (ADTKD) are characterized by progressive renal failure culminating in end-stage renal disease, with non-specific structural changes including interstitial fibrosis and tubular atrophy. Mutations in UMOD, the gene that encodes uromodulin, the most abundant protein in normal urine, are predominantly involved. More recently, mutations in three additional genes, HNF1B, REN and MUC1, have also been associated with ADTKD. The relative prevalence of the underlying genetic defect and the clinical criteria for genetic testing in ADTKD remain to be defined.

Methods: We recruited 133 Belgian and Swiss families presenting tubulointerstitial nephritis with either gout or hyperuricemia before the age of 40 years, renal cysts or a first degree relative with tubulointerstitial nephritis. We included the cases in a comprehensive registry and screened all families for UMOD mutations, followed by screening for HNF1B and REN mutations in UMOD-negative families.

Results: We detected mutations in UMOD in 44 out of 133 (33%) tested families. Among the UMOD-negative families, 5 out of 77 (6.5%) screened positive for HNF1B mutations and none was positive for REN mutations. We analyzed the UMOD mutations and found that 86% of them are clustered in exon 3 and that 43% involve conserved cysteines crucial for the tertiary structure of uromodulin. We retrospectively detected a strong positive correlation between early hyperuricemia/gout and the rate of UMOD mutation detection (fig. 1).

Conclusions: Mutations in UMOD were detected in 33% of tested families with ADTKD, contrasting with low detection rates for HNF1B and REN mutations in UMOD-negative families in this cohort (6.5% and 0%, respectively). The rate of UMOD mutation detection is strongly correlated with early hyperuricemia/gout. The role of MUC1 remains to be ascertained. The creation of this registry will be useful to delineate the genetic and clinical spectrum of ADTKD in Switzerland and beyond.

Figure 1
Rate of UMOD mutation detection according to the number of clinical criteria.

Long term outcome of membranous glomerulonephritis 
associated with anti-PLA2R antibodies
Helmut Hopfer1, Thomas Menter1, Elion Hoxha2
1Institute of Pathology, University Hospital Basel, Basel, Switzerland; 2Clinic for transplant immunology and nephrology, University Hospital Basel

Most cases of primary membranous glomerulonephritis are caused by autoimmunity against the phospholipase A2 receptor (PLA2R). Detection of circulating antibodies against PLA2R and immunohistochemical PLA2R staining can be used to identify these patients. Long term data regarding the outcome have not been reported.

We retrospectively analyzed patients with primary or secondary MGN diagnosed at the University Hospital Basel between 1992 and 2007. Kidney biopsies were stained for PLA2R by immunohistochemistry. Serum taken at the time of biopsy was tested for anti-PLA2R antibodies. Clinical follow-up data were collected and, if possible, patients were retested for anti-PLA2R antibodies.

34 patients (21 male, 13 female, median age 61.9 years) were identified and enrolled in the study. 27 were considered to have primary MGN. By indirect immunofluorescence tests, 18 had circulating anti-PLA2R at the time of diagnosis, 16 of them also showing a positive biopsy staining. Two of 9 patients with negative serum tests still had a positive immunohistochemistry. A positive antibody titer significantly correlated with a positive immunostaining (p <0.01). Follow-up data were available for 21 primary MGN patients. Three of these developed end-stage renal disease. 14 of the remaining patients were retested for anti-PLA2R antibodies after a median follow-up of 9.5 years (5.2–19.3). Only 3 patients still had detectable circulating autoantibodies. Compared to the patients that had turned negative during follow-up, they tended to have higher proteinuria (2.6 g/day vs. 0.45 g/day, p = 0.18). Immunosuppressive treatment had neither a positive effect on GFR nor on proteinuria at the end of follow-up.

Our data show that both detection of antibodies in the serum and immunohistochemistry are useful to identify MGN patients with an autoimmune response against PLA2R. Most of these patients will control the antibody response during the course of the disease with a favorable outcome, even without therapy.
Sleep quality decreases with declining GFR in early stages of chronic kidney disease
Adam Ogna*, Valentina Forni Ogna*, José Haba Rubio1, Nadia Tobbback2, Monelle Bochud3, Raphaël Heinzer1
1Center for Investigation and Research in Sleep (CIRS), University Hospital of Lausanne (CHUV), Lausanne, Switzerland; 2Service of Nephrology and Hypertension, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; 3Community Prevention Unit, University Institute of Social and Preventive Medicine (IUMSP), Lausanne, Switzerland
*Valentina Forni Ogna and Adam Ogna: Joint First Authorship

Introduction: Sleep disturbances are a common complaint in end stage renal disease patients. We assessed sleep quality in early CKD stages in comparison to the non-CKD subjects, and evaluated their association with kidney function.

Methods: 1747 participants in the population-based HypnoLaus study (857 men, 890 women) underwent full polysomnography at home and answered a questionnaire on their sleep quality. Glomerular filtration rate (GFR) was estimated by CKD-EPI equation and categorized according to KDIGO2012 guidelines. Only subjects with GFR <30 ml/min were considered. Associations of SSQ and sleep efficiency with GFR categories were explored by logistic and linear regression, respectively.

Results: Mean age of the population was 59.2 (±11.3) years and mean GFR 82.1 (±14.7) ml/min/1.73 m2. 269 (15.4%) subjects had a CKD: 8.3% St1-2 and 71.3% St3. 48% of patients with CKD-St3 vs 39% with no-CKD reported poor subjective sleep quality (SSQ, p = 0.05). They had shorter total sleep time (TST: 384 ± 80 min vs 402 ± 71, p = 0.008) and lower sleep efficiency (SE: 78 ± 12% vs 85 ± 11, p <0.001) compared to non-CKD. CKD-St1-2 patients showed intermediate features (p <0.001 for trend across CKD stages, for both TST and SE). The use of sleep medication increased across CKD stages (9.6%, 11.1% and 14.9% for no-CKD, St1-2 and St3 respectively, p = 0.02 for trend).

Older age and the severity of sleep apnea were the strongest predictors of both poor SSQ and low SE in multivariate regression analysis adjusting for gender, periodic leg movements during sleep and restless legs syndrome; CKD-St3 was significantly associated with a reduced SE (p = 0.03) but not with subjective sleep quality in the preceding models.

Conclusion: Low GFR in early stages of CKD is associated with impaired subjective and objective sleep quality, and with increased consumption of sleep medication. Besides classical factors, such as age and sleep apnea, kidney function level below CKD-stage 3 seems to negatively affect sleep quality.

Correlation of Transcriptome Sequencing Data from Formalin-Fixed, Paraffin-Embedded vs. RNAlater® stored Kidney Biopsies
Oystein Ekrem1, Christian Beisland1, Karin Hjelte1, Anar Flatberg2, Andreas Scherer1, Heidrun Vethe1, Trude Skogstrand2, Sabeen Leht3, Vidar Beisvang1, Hans-Peter Marti1, Department of Pathology, University of Bergen, Bergen, Norway; 2Department of Clinical Medicine, Urology, University of Bergen, Bergen, Norway; 3Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway; *Spheromics, Kontiolahti, Finland; *Department of Pathology, University of Bergen, Bergen, Norway

Background: Archival, formalin-fixed, paraffin-embedded (FFPE) kidney biopsies are a readily available although underused resource for molecular diagnostics. This feasibility study aimed to establish next generation sequencing (NGS) from these biopsies.

Methods: Core biopsies were obtained with a 16 g needle from 6 patients undergoing (partial) nephrectomy at time of surgery. Paired biopsies from each patient with histologically-confirmed clear cell renal cell carcinoma (ccRCC) and non-tumorous (“normal”) tissue were either FFPE or stored in an RNA-stabilizing agent (RNAlater®, Qiagen, Germany). Total RNA was extracted with the miNeasy FFPE kit or the miRNAeasy FFPE kit (Qiagen), respectively. NGS libraries were prepared using the Illumina TruSeq® RNA Aconola protocol and sequenced on an illumina HiSeq 2500 instrument. Assembly of reads and alignment of the contigs was guided by TopHat and Bowtie. Comparative analysis was done using voom/Limma R-package.

Results: Analysis of the FFPE and the RNAlater® datasets yielded similar numbers of detected RNA species, differentially expressed transcripts and significantly affected pathways. The average expression of detected transcripts in both datasets correlated very well (R2 = 0.96), and log2 fold changes of the transcripts were significantly altered in both datasets (padj <0.05, fold changeabs ≥ 2; n = 920) correlated with R2 = 0.94. Among the transcripts with the highest fold changes in both datasets were NPTX2 and CA9, both higher expressed in tumor, and UMOD, higher expressed in non-tumor tissue. All three genes are known to be differentially regulated in ccRCC.

In both datasets, pathway analysis reveals the presence of gene signatures of cancer, renal damage and immune response. Immunohistochemistry confirmed the down-regulation of uromodulin (UMOD) in ccRCC. In essence, we have obtained a ccRCC signature according to the literature in both data sets.

Conclusions: NGS is feasible in FFPE kidney biopsies and expands the utility of these tissue specimens.

Effect of SGLT-2 inhibitor Dapagliflozin on Cystic Disease Progression in PCK Rats with Intrafamilial Recessive Polycystic Kidney Disease (ARPKD)
Sarika Kapoor1, Daniel Rodriguez1, Meliana Riwanto2, Ilka Edenhofer3, Stephan Segerer1, Katharyn Mitchel1, Colin Schwarzwald1, Rudolf P. Wüthrich1, Division of Nephrology, Emory University school of Medicine, Atlanta, USA; *Division of Nephrology, University Hospital, Zurich, Switzerland

Background: Autosomal dominant polycystic kidney disease (ADPKD) accounts for 5% of patients with end stage renal disease (ESRD). As specific treatment options are likely becoming available in the near future, predicting disease course would be of utmost importance to select high risk patients for treatment. We have previously identified ADPKD-specific patterns of urine peptide excretion but have not been able to predict disease course so far. Here, based on extended follow up time, we identified a set of urinary peptides that predict progression to ESRD and thus allow early detection of high risk ADPKD patients.

Methods: Baseline urine samples from all patients in the CRISP cohort were analyzed by capillary electrophoresis online coupled to mass spectrometry (CE-MS). All patients were followed for up to 12 (minimum 7) years and the urine peptide profile of those reaching ESRD was compared to control patients with relatively slow progression during follow up (defined as an annual GFR loss of no more than 4 ml/min/1.73 m2). Two thirds of both cases and controls were used to identify a prognostic biomarker score, the remaining patients served as validation cohort.

Results: During follow up, 22 patients reached ESRD, and 46 patients matched for baseline GFR had a low progression rate. A prognostic biomarker score based on 52 urinary peptides, applied to the validation cohort, reached an AUC of 0.94 in the training cohort upon cross validation and an AUC of 0.81 in the validation cohort to identify patients reaching ESRD during follow up (sensitivity 83% and specificity 71% at a predetermined cut-off level).

Conclusions: We identified a biomarker score based on the urine peptide profile at a single timepoint that allows to identify ADPKD patients with high risk for future progression to ESRD.
Blood and urine were collected at baseline and after 3 and 6 weeks of treatment to assess parameters of renal function. After 6 weeks of treatment, ultrasound was performed and rats were immediately sacrificed and kidneys were excised for analysis of cyst growth.

Results: DAPA significantly increased urine output (DAPA 57.3 ± 19.2, CON 19.3 ± 2.3 ml/day at week 6 of treatment) and resulted in higher osmolar excretion (DAPA 62.5 ± 15.8, CON 23.9 ± 2.8 mosm/day) and higher glucose excretion (DAPA 23.4 ± 12.0, CON 0.3 ± 0.3 mmol/ day). After 3 weeks of treatment, DAPA-treated PK rats displayed higher clearances for creatinine (DAPA 3.06 ± 0.40, CON 2.56 ± 0.54 ml/min) and BUN (DAPA 1.71 ± 0.34, CON 1.23 ± 0.31 mmol/l) whereas after 6 weeks there was no difference between DAPA and CON. Furthermore, DAPA-treated PK rats displayed a 3.5-fold increase in albumin excretion after 6 weeks of treatment. Surprisingly, there was a 23% higher total kidney weight after 6 weeks of treatment with DAPA. In vivo ultrasound imaging and histological analysis also showed an increase in the cyst growth, although there was no change in the level of renal cAMP content between both groups.

Conclusions: Inhibition of glucose reabsorption with the SGLT2-specific inhibitor DAPA caused significant glycosuria, hyperfiltration and albuminuria in PK rats. Unexpectedly, the cyst growth was enhanced, suggesting that the factors which regulate cyst growth in this model act independently from the factors which control GFR. The mechanisms which link glycosuria and hyperfiltration to distal cyst growth remain to be elucidated.

Calciprotein Particles Induce Calcification of Vascular Smooth Muscle Cells In vitro

Parisa Aghagolzadeh1, Bijamia Rakesh Kumar1, Prakash Chandak1, Matthias Bachtler2, Edward R. Smith3, Andreas Pasch4
1Department of Nephrology, Hypertension, and Clinical Pharmacology, Inselspital, University of Bern, Switzerland; 2Department of Nephrology, The Royal Melbourne Hospital, Melbourne, Australia

Background: Calciprotein particles (CPP) are calcium phosphate-containing nano-aggregates which have been found in the blood of CKD patients. The effect of CPP on vascular smooth muscle cells (VSMC) mineralization has yet to be evaluated.

Methods: Synthetic primary and secondary CPP were generated using phosphate-enriched culture medium (DMEM/10% FBS) incubated at 37 °C for either one day (primary CPP) or seven days (secondary CPP). Human VSMC were cultured with these media and mineralization was assessed quantitatively by Alizarin red staining and qualitatively by measurement of calcium and phosphate content.

Results: The supplementation of culture medium with 3.5 mM phosphate and 1 mM calcium resulted in a time- and temperature-dependent generation of primary and secondary CPP, as identified by TEM. Exposure of VSMC to secondary CPP led to a pronounced and consistent dose-related accumulation of calcium and phosphate mineral (i.e. calcification) within 5 days, whereas exposure to primary CPP did not. Furthermore, the amount of FBS used for the generation of morphologically indistinguishable secondary CPP corresponded to the extent of VSMC calcification.

Conclusion: CPP form spontaneously in cell culture medium containing high phosphate. Secondary CPP induce VSMC calcifications in vitro, whereas primary do not. This indicates that controlling CPP particle type and transformation may be an important determinant of VSMC calcification in vitro.

The sodium/proton exchanger NHA2 is a novel regulator of sodium and calcium homeostasis in the distal convoluted tubule

Manuel Andergag1, Giuseppe Albano1, Christine Deil2, Ganesh Pathare3, Johannes Loffing4, Alain Vendewalle5, Daniel Fuster2
1Institute of Biochemistry and Molecular Medicine, University of Bern and Division of Nephrology, Hypertension and Clinical Pharmacology, University Hospital of Bern, Switzerland; 2University of Zurich, Institute of Anatomy, University of Zurich, Zurich, Switzerland; 3Inserm, Centre de Recherche Biomédicale Bichat Beaujon, Paris, France

NHA2 is a recently cloned sodium/hydrogen exchanger present in all metazoan genomes with unknown biological function. We recently demonstrated that NHA2 is critical for insulin secretion in β-cells (Deisl et al., PNAS 2013). Here we find that NHA2 is expressed in distal convoluted tubules of mice and humans, a tubular segment that is paramount for the regulation of sodium, calcium and blood pressure homeostasis. To test the potential physiological role of NHA2 in the kidney, we performed telemetric blood pressure measurements and metabolic balance studies in NHA2 WT and KO mice. NHA2 was dispensable for the renal adaptation to acute metabolic acidosis and water deprivation. Blood pressure, however, was lower in NHA2 KO mice compared to WT mice under high sodium diet, but not under low sodium diet. In addition, NHA2 KO mice exhibited normocalcemic hypocalciuria with lower plasma PTH levels while 1,25-DH OH Vitamin D3 levels remained unaltered. Interestingly, immunoblotting of kidney lysates revealed significantly reduced phosphorylation of the thiazide-sensitive sodium/chloride co-transporter (NCC), mutated in Gitelman’s syndrome, in the distal convoluted tubules of NHA2 KO mice. Similarly, phosphorylation of the SPS1-related proline/alanine-rich kinase (SPAK), the kinase responsible for NCC phosphorylation, as well as the abundance of WNK4, a kinase further upstream in the regulatory cascade of NCC phosphorylation, was markedly reduced in kidney lysates of KO mice compared with those of WT mice. In line with these findings, NHA2 KO mice exhibit a reduced natriuretic response to hydrochlorothiazide compared to WT mice. In the distal tubular cell line mpkDC6T4, stimulation of NCC phosphorylation is reduced upon siRNA-mediated knockdown of NHA2, compared with control siRNA-treated cells. Thus, in summary, our data reveal the sodium/hydrogen exchanger NHA2 as a novel regulator of calcium, sodium and blood pressure homeostasis in the distal convoluted tubule of the kidney.

Calcification propensity after kidney donation: a one year prospective study

Belen Ponte1, Karine Hadaya2, Pierre-Yves Martin1, Andreas Pasch2, Sophie de Seigneur2
1Service of Nephrology, Department of Specialties, University Hospital of Geneva, Geneva, Switzerland; 2University Hospital of Bern

Background: The question of increased cardiovascular risk after kidney donation is still a matter of debate. Recently, a novel nanoparticle-based test was developed to measure overall calcification propensity in serum. When applied to predialysis CKD patients, high calcification propensity (i.e. low T50) was associated with progressive aortic stiffening and increased future all-cause mortality at a follow up of five years. In this work, we investigated the impact of kidney donation on serum calcification propensity (T50).

Methods: We included 21 living kidney donors (LKD) in a prospective study. We measured T50, augmentation index (AI) renal resistance index (RRI) and pulse wave velocity (PWV) before donation, and at 12 months after donation.

Results: T50 showed a significant decline in renal function (95 ± 10 versus 61 ± 11 ml/min/1.73 m², p <0.001) and plasma phosphate levels (12 ± 0.2 versus 11.1 ± 0.2 mmol/l, p <0.005) compared to predonation after one year of follow up. T50 measurement increased slightly one year after donation (290 ± 53 versus 312 ± 38 min, p = 0.0495).

AI, PWV as well as RRI were not changed significantly by kidney donation. Correlation analyses revealed no significant associations between T50, AI, RRI and PWV (all p >0.09), neither at baseline nor after one year. However, T50 was inversely correlated to plasma phosphate level (R = −0.64, p = 0.002 at day 0 and R = −0.48, p = 0.03 at 1 year).

Conclusion: We demonstrate that one year after kidney donation, calcification propensity slightly improves whereas PWV and RRI are unchanged in kidney donors compared to predonation. This supports the notion that the loss of NHA2 associated with kidney donation does not per se enhance cardiovascular risk.

Final Results from the Long-term Extension (LTE) of the Belatacept Phase 2 Study in Kidney Transplantation

Flavio Vincenti1, Christian Larsen2, Josep Grinyó3, Ferdinand Mühlbacher4, Sophie de Seigneur5, Prakash Chandak3
1University of California at San Francisco, USA; 2Emory University, USA; 3University Hospital of Bellvitge, Spain; 4Medical University of Vienna, Austria; 5University Hospital of Nantes, France; 6Medizinische Hochschule Hannover, Germany; 7Bristol-Myers Squibb, USA; 8University Hospital of Bicêtre, France

Background: At 5 years post-transplant, data from the Phase 2 IM013-100 LTE study of belatacept (belia) in kidney transplantation demonstrated a favorable safety profile and improved renal function vs cyclosporine (CsA) (Vincenti F et al., JASN 2010;21(9):1587–96).
Here we report outcomes in all randomized and treated patients through study close (approximately 10 years).

**Methods:** 218 patients were randomized to receive bela (n = 145) or CsA (n = 73). After 6 months, bela patients were randomized to 4-week (n = 62) or 8-week (n = 60) dosing intervals (5 mg/kg). Here we focus on the results from randomization to study end in bela patients randomized to 4- or 8-week treatment groups and all CsA patients.

**Results:** At month 3, mean MDRD cGFR was 66 (bela 4-week), 65 (bela 8-week), and 60 (CsA) mL/min/1.73 m²; and at 10 years mean cGFR was 72 (bela 4-week), 67 (bela 8-week), and 52 (CsA) mL/min/1.73 m² (figure). From randomization to end of study, acute rejection occurred in 4, 4, and 5 patients in the bela 4-week, bela 8-week, and CsA groups, respectively. Death or graft loss occurred in 14 bela patients (10%) and 8 CsA patients (11%). The incidence rate of serious adverse events was 33 (bela 4-week), 48 (bela 8-week), and 55 (CsA) per 100 person-years; incidence of serious infections was 6 (bela 4-week), 10 (bela 8-week), and 15 (CsA) per 100 person-years. There were 3 cases of PTLD in bela-treated patients (2 EBV-negative, 1 EBV-unknown) that occurred by Month 13 and 1 case in a CsA-treated patient in Year 4 (EBV-unknown).

**Conclusions:** Data from this limited cohort suggest that the profile of bela is consistent over approximately 10 years of treatment: patients maintained renal function with no new safety findings, and long-term outcomes were similar between 4-week and 8-week treatment groups. Results should be validated in a larger cohort.

---

### Summary of Calculated GFR Over Time (MDRD formula; as Observed):

<table>
<thead>
<tr>
<th>Patients with measurements:</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
<th>108</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belatacept 4-wk</td>
<td>61</td>
<td>59</td>
<td>58</td>
<td>49</td>
<td>46</td>
<td>44</td>
<td>43</td>
<td>40</td>
<td>34</td>
<td>37</td>
<td>33</td>
</tr>
<tr>
<td>Belatacept 8-wk</td>
<td>58</td>
<td>57</td>
<td>55</td>
<td>42</td>
<td>40</td>
<td>35</td>
<td>36</td>
<td>33</td>
<td>34</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>CsA</td>
<td>65</td>
<td>65</td>
<td>50</td>
<td>17</td>
<td>18</td>
<td>14</td>
<td>13</td>
<td>12</td>
<td>10</td>
<td>11</td>
<td>9</td>
</tr>
</tbody>
</table>

*Only patients randomized to belatacept 4-wk/8-wk schedules are included. cGFR = calculated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease

---

**Why are potential living kidney donors declined?**

1. Aurelia Schnyder¹, Dimitrios Tsinalis¹, Wolfgang Ender¹, Jutta Thierbach², Urs Stillhard³, Isabelle Binet¹

1Klinik für Nephrologie und Transplantationsmedizin, Kantonsspital St. Gallen; ²Regionales Blutspendezentrum St. Gallen; ³Klinik für Psychosomatik, Kantonsspital St. Gallen

**Background:** Within the last decades living kidney donation has become an important part of every renal transplantation program. As a relevant number of potential donors is declined in the process, we analysed the reasons for not being a suitable donor.

**Methods:** All potential living donors evaluated at our center between 2007 and 2013 were examined, including non-directed donors. Evaluation followed the principles recommended by the SAMW (Swiss academy of medical sciences). The reasons for declining donation were recorded prospectively and analysed.

**Results:** A total of 139 potential donors was evaluated, resulting in 33 transplantations and 106 donors being declined. Accepted donors were on average 53 years old and 68% were females. Declined donors were on average 52.5 years and 58% females (not significant vs. accepted donors).

The main reasons for declining were immunological (34%, due to donor specific antibodies and/or positive crossmatch), followed by psycho-social (16%) and renal (13%) conditions. Half of these were donor specific antibodies and/or positive crossmatch, followed by obesity (3%) led to declining donation.

**Conclusions:** Despite ABO incompatible transplantation, immunological reasons for declining donation still make up to one third of the cases.

---

**The C1q-binding assays and clinical outcomes in kidney transplantation**

Gideon Hönger¹, Helmut Hopfer², Stefan Schaub³, Robert Liwski³, Patrizia Amico¹

1Transplantation Immunology and Nephrology, University Hospital Basel, Switzerland; ²Institute for Pathology, University Hospital Basel, Switzerland; ³Department of Pathology and Laboratory Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

**Background:** Contradictory conclusions have emerged from clinical trials when testing the predictive value of C1q-binding donor-specific HLA-antibodies (HLA-DSA). The aim of this study was to investigate the association between C1q-binding ability of HLA-DSA and the clinical outcome (i.e. antibody-mediated rejection (AMR) and long-term allograft survival).

**Methods:** Pretransplant sera of 64 patients known to possess preformed HLA-DSA were retrospectively analyzed by the standard and anti-globulin (AHG) enhanced C1q assay.

**Results:** The cumulative incidence of clinical/subclinical AMR within 8-week, and CsA groups, respectively. Death or graft loss occurred in 14 bela patients (10%) and 8 CsA patients (11%). The incidence rate of serious adverse events was 33 (bela 4-week), 48 (bela 8-week), and 55 (CsA) per 100 person-years; incidence of serious infections was 6 (bela 4-week), 10 (bela 8-week), and 15 (CsA) per 100 person-years. There were 3 cases of PTLD in bela-treated patients (2 EBV-negative, 1 EBV-unknown) that occurred by Month 13 and 1 case in a CsA-treated patient in Year 4 (EBV-unknown).

**Conclusions:** Data from this limited cohort suggest that the profile of bela is consistent over approximately 10 years of treatment: patients maintained renal function with no new safety findings, and long-term outcomes were similar between 4-week and 8-week treatment groups. Results should be validated in a larger cohort.

---

**Why are potential living kidney donors declined?**

*OC 11*

---

**The C1q-binding assays and clinical outcomes in kidney transplantation**

*OC 12*
posttransplant was also not different between the recipients with and without C1q-binding HLA-DSA: p >0.05, p >0.35, and p >0.35 for the standard C1q assay; p >0.20, p >0.20, and p >0.10 for the AHG C1q assay with the cut-offs MFI 300, 500, and 1000. At a median of 8 years posttransplant, allograft survival was equal in patients with/without C1q-binding HLA-DSA (p >0.57 for the standard and p >0.09 for the AHG enhanced C1q assay). The MFI was a strong and independent factor for C1q-binding in both C1q assays (OR >8.25 for standard and >4.33 for AHG enhanced C1q assay; p <0.0001).

Conclusion: Pretransplant C1q-binding HLA-DSA – either detected by the standard or the AHG enhanced C1q assay - were not predictive for any clinical outcome. The MFI of HLA-DSA was strongly influencing C1q-binding.

Human Proximal Tubule Cells Form Functional Microtissues

Jenny Kürth1, Manuela Bieni2, Wolfgang Montz2, Olivier Devuyts1

1Institute of Physiology, University of Zurich, Switzerland; 2Insphero AG, Zurich, Switzerland

Background: The epithelial cells lining the proximal tubules (PT) of the kidney mediate complex transport processes that are particularly vulnerable to drug toxicity. Two-dimensional cultures of immortalized PT cells have been used in drug toxicity research, prior to animal trials. Since this approach does not reproduce the physiological conditions (e.g. saturable endocytic uptake) encountered in vivo, generating three-dimension organotypic microtissues has become an important objective for drug safety and toxicity studies.

Methods: Microtissues cultures of PT cells (immortalized and primary) were done in hanging-drop GravityPLUS® culture plates under objective for drug efficacy and toxicity studies.

Results: Kidney microtissues were successfully obtained by co-culturing fibroblasts with immortalized human proximal tubular cells (HK-2) or Human Renal Proximal Tubular Epithelial Cells (HRPTEpC) in hanging-drop plates. The HK2 microtissues formed highly proliferative, but dedifferentiated microtissues within 10 days of culture, while co-culture with fibroblasts yielded spherical structures already after 2 days. Low passage HRPTEpC microtissues (pure and co-culture) were less proliferative and expressed tissue-specific differentiation markers important for functional readout. Electron microscopy analysis showed more evident markers of epithelial differentiation (microvilli and tight junctions) in the co-cultured HRPTEpC microtissues. The functionality of HRPTEpC microtissues was evidenced by the endocytic uptake of Alexa 488-labelled albumin.

Conclusion: We established a reliable hanging-drop protocol to obtain kidney microtissues with different PT cell lines. Microtissues obtained by this approach could be used for the development of high throughput drug and toxicology screenings, using endocytosis as a functional readout.

Fetal hypoxia induced ectopic Fetuin A expression in renal tubular cells

Stefan Rudloff1, Stephane Rodriguez2, Uyen Huynh-Do1

1Department of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Bern University Hospital, Department of Clinical Research, University of Bern, Switzerland; 2University of Rennes, France

Background: In previous experiments, we demonstrated that hypoxia during fetal development induces intrauterine growth restriction. Further, microarray analysis showed upregulation of Fetuin A in the kidneys of hypoxic embryos. In this study, we examined whether Fetuin A, which is normally secreted only by the liver, is produced locally in the hypoxic kidney.

Methods: Pregnant mice were exposed to hypoxic condition (9.5% O2) from E14.5 until E18.5, sacrificed, and fetal kidneys were collected for analysis: Whole mount in situ hybridization (WISH) using 2 different riboprobes directed against the 3' or 5' half of Fetuin A mRNA, immunohistochemistry (IHC), Western blot and qRT-PCR.

Furthermore, the Fetuin A promoter region was analyzed for hypoxia-responsive elements using BIOBASE and TRANSFAC® positional weight matrices with the Patch 10.0 algorithm.

Results: Fetuin A was detected by Western blot and qRT-PCR only in hypoxic kidneys, but not in normoxic controls. Both riboprobes gave a similar expression pattern of Fetuin A in tubular structures traversing the renal cortex and extending into the deeper layers of whole mount hypoxic kidneys. In WISH or IHC sections, these structures were identified as distal tubules and collecting ducts. Analysis of the Fetuin A promoter region identified two potential binding sites for Hif-1 at -2kb and +1.5 kb relative to the transcription start site.

Conclusions: Hypoxia imposes a severe stress condition on the developing renal cells. Fetuin A is a serum protein, normally secreted by the liver, which is the major anti-calcification agent in the serum. Based on our findings, we hypothesize that in response to hypoxia, renal tubular cells produce Fetuin A, which might protect the developing kidney from calcifying. Further studies using Fetuin A knock-out animals are planned to substantiate this hypothesis.

A role for hypoxia-inducible cytoglobin in chronic kidney disease?

Elsa Rand1, Sara Santambrogio2, Maja Lindenmeyer2, Federica Starti2, Clement Cobin1, Olivier Devuys1, Andreas Kisters1, Roland Wenger1, David Hoogewijs3

1University of Zurich, Institute of Physiology; 3Division of Nephrology, University Hospital, Zurich, Switzerland; 2Institute of Physiology, University of Duisburg-Essen, Essen, Germany

Background: Cytoglobin (CYGB) is a recently discovered globin that belongs to the mammalian globin family, in addition to hemoglobin and myoglobin. Despite extensive research efforts, its physiological role remains unknown, but possible functions include reactive oxygen species (ROS) detoxification and signaling. Accumulating evidence suggests that ROS play a crucial role in podocyte detachment and/or apoptosis during diabetic nephropathy.

Methods: To assess the putative anti-oxidative function of CYGB in podocytes, we are using the human podocyte cell line A8b13, which expresses high endogenous CYGB levels. We generated stable CYGB knock-down and overexpressing cell models and are currently studying CYGB-dependent gene expression, cell viability and oxidative stress response.

Results: CYGB deficient cells showed an increase in cell death, up-regulation of pro-apoptotic gene expression and are more sensitive to oxidative stress compared to CYGB overexpressing podocytes. Interestingly, gene array expression analysis of biopsies from CKD patients showed a pronounced CYGB induction in diabetic nephropathy, validated by RT-qPCR in independent nephropathy samples. Moreover, genome-wide association studies (GWAS) revealed that CYGB is potentially implicated in chronic kidney disease (CKD).

Conclusions: Data of our study demonstrate for the first time that CYGB (i) is expressed in a human podocyte cell line, (ii) protects podocytes from oxidative stress and apoptosis, and (iii) may be involved in CKD, particularly in diabetic nephropathy. In parallel to validating our findings in an independent podocyte model we will study the CYGB-dependent transcriptome, to gain further functional insight in the molecular mechanism of CYGB in podocytes.

Mechanism of coupling between trancellular sodium transport and paracellular permeability in renal collecting duct cells

Eric Feraille1, Yubao Wang1, Isabelle Roth2, Thomas Ermacora1, Eva Bernabei1

1University of Geneva

The aldosterone-sensitive distal nephron is responsible for the fine-tuning of sodium balance. According to dietary sodium intake, collecting ducts (CD) are subjected to large variations of sodium transport. In CD, sodium reabsorption occurs mostly through principal cells via a tranacellular pathway that involves apical channels (ENaC) and basolateral Na,K-ATPase. Several strands of tight junctions prevent paracellular ion permeability and sodium back flux. We hypothesized that tranacellular sodium fluxes cross talk with tight-junctions to prevent back flux of reabsorbed ions. We analyzed cultured mCCDcl1 cells either subjected to aldosterone treatment or doxycycline-inducible overexpression γ-ENaC to increase tranacellular sodium flux. Increased tranacellular sodium transport was associated with enhanced transepithelial resistance. Time-course experiments revealed that current increased first followed by increased transepithelial resistance. Total and Triton X-100 insoluble claudin-4 and 8 protein abundance were increased. However, only claudin-8
mRNA levels were increased indicating that a primary increase in claudin-8 protein level may secondarily stabilize claudin-4. The increase in claudins abundance relied on decreased β-catenin signaling and was prevented by inhibition of GSK3. In addition, abundance of membrane associated β-catenin increased thus decreasing availability of cytoplasmic β-catenin for nuclear translocation. These results were confirmed in aldosterone-treated rats subjected to either low or high dietary sodium. In this setting, higher levels of sodium reabsorption in the CD were associated with increased claudin-8 protein abundance.


Methods: Mutations in the V-ATPase B1 subunit gene ATP6V1B1 cause autosomal-recessive distal renal tubular acidosis. We previously demonstrated that a common single nucleotide polymorphism (SNP) in ATP6V1B1 (c.481G>A; p.E161K) greatly diminishes pump function when tested in vitro. To study the impact of the p.E161K SNP on urinary acidification in humans, we conducted a cross-sectional study in the Dallas and Bern kidney stone registries.

Methods: Inclusion criteria: informed consent and at least one stone episode. Exclusion criteria: Hyperparathyroidism, cystinuria, idiopathic hypercalciuria, diabetes, renal calculi with a subtype other than CaP, patients under 18 years of age, patients with kidney diseases. We tested whether altered NCC activity with kidney diseases. We tested whether altered NCC activity

Results: 550 stone formers (SF) could be included. 32 of the 550 SF (5.8%) were heterozygous for the SNP. No patient in these cohorts was homozygous for the SNP. Mean age at presentation was 43.6 years in wild-type and 38.5 years in heterozygous SF (p < 0.05). Plasma HCO3- was not different between the two groups. However, on a random outpatient diet, heterozygous SF had significantly higher 24 hr urinary pH (6.31 vs 6.09; p < 0.05) and lower 24 hr urinary citrate excretion (2.23 vs 3.00 mmol; p < 0.05). On an outpatient diet restricted in Na+ and Ca2+, the difference in 24 hr urinary pH became even more pronounced (6.44 vs 6.04; p < 0.001). Compatible with the findings of increased urinary pH, calcitriol of heterozygous SF were more likely to contain calcium phosphate (CaP; p < 0.05).

Conclusions: SF with the V-ATPase B1 subunit p.E161K SNP are younger at presentation and exhibit a urinary acidification deficit with an increased prevalence of CaP containing kidney stones. The burden of E161K heterozygosity may be a forme fruste of distal RTA.

Dietary phosphate intake increases blood pressure via the NCC cotransporter ("(NCCR) Project")

Arezoo Daryadel, Isabel Rubio Aliaga, Johannes Loffing, Carsten Wagner.

1University of Zurich, Institute of Physiology; 2University of Zurich, Institute of Anatomy, University of Zurich, Zurich, Switzerland

Background: The thiazide-sensitive Na+/Cl- cotransporter NCC, located in the apical membrane of epithelial cells lining the distal convoluted tubule of the kidney and is important for fine-tuning of renal sodium reabsorption via NaCl and therefore detection of renal NCC abundance is of great interest.

Methods: The aim of the present study was to investigate the effect of antihypertensive treatment on NCC abundance. Firstly using novel technique of analyzing urinary oxosomes we characterized expressions of the NCC in six healthy subjects. Furthermore, urinary oxosomes of patients with essential hypertension (n = 23) before and after hydrochlorothiazide (HCT) and Valsartan treatment were characterized for NCC and its phosphorylated form (pNCC) expression. Patients were monitored for clinical biochemistry and 24-hour ambulatory blood pressure.

Results: NCC was detected in urinary oxosomes as a glycosylated protein forming an oligomeric structure. It comprised of dimer (≈ 250 kDa) and monomer (≈ 125 kDa). Despite of its inhibitory nature, HCT treatment led to a more than 2 fold increase in NCC and pNCC expression. On the other hand, Valsartan treatment did not significantly affect oxosomal NCC or pNCC abundance. The amount of CD9, an oxosomal marker, was similar after all treatments.

Conclusions: We found that chronic HCT treatment in hypertensive patients increased NCC and pNCC expression within urinary oxosomes. Our results support the notion that NCC abundance in urinary oxosomes can be employed as a clinical biomarker for the detection of salt-sensitive hypertension.
Activation of the transcription factor Nrf2 attenuates the pro-inflammatory response of mouse macrophage following CPP exposure: Potential therapeutic target in vascular calcification (NCCR Project)

Adam Lister¹, Philippe Marbel¹, Thomas Hammond¹, Ian Copple², Prakash Chandak³, Andreas Pasch³, Christopher Goldring³, Alex Odermatt³
¹Division of Molecular and Systems Toxicology, Department of Pharmaceutical Sciences, University of Basel, Switzerland; ²MRC Centre for Drug Safety Science, Department of Molecular & Clinical Pharmacology, University of Liverpool, Liverpool, UK; ³Department of Nephrology and Hypertension, University Hospital and University of Bern, Switzerland

Background: Fetuin-A-containing calciprotein particles (CPP) clear calcium from the blood, leading to the reticuloendothelial system, thus preventing soft tissue mineralization. Increased levels of CPP in pathological situations can trigger the generation of reactive oxygen species (ROS) and inflammation, two of the underlying causes leading to vascular calcification. The transcription factor, nuclear-factor-E2-related factor 2 (Nrf2) is a master regulator of cell defense and can protect against oxidative and electrophilic stress. Under normal basal conditions, Nrf2 is repressed in the cytoplasm by its inhibitor Keap1, which subsequently targets Nrf2 for ubiquitination and proteosomal degradation. We hypothesized that the induction of Nrf2 in macrophage may be a beneficial target to inhibit the progression of calcification by preventing CPP driven inflammation.

Methods: The mouse Raw 264.7 cell line was used as a model macrophage. We exposed the cells to CPP and measured the expression of the pro-inflammatory M1 markers MCP1, IL1-β and TNF-α by quantitative RT-PCR and ELISA. We manipulated the Nrf2/Keap1 system using a well characterized synthetic Nrf2 inducer, CDDO-Me, and also knocked down the expression of Nrf2 and Keap1 using specific siRNA targeting molecules.

Results: We show that CPP induce a strong proinflammatory response in Raw 264.7 cells increasing the transcription and secretion of MCP1, IL1-β and TNF-α. The expression of MCP1 and IL1-β, but not that of TNF-α, was strongly suppressed by CDDO-Me and Keap1 knockdown via the Nrf2 pathway.

Conclusions: Macrophage-specific Nrf2 induction may ameliorate the secondary CPP driven inflammatory response and therefore delay the progression of calcification.

---

Abdominal CT scan in 30 EPS patients prior to surgery: a tool to predict the intraoperative findings?

Daniel Kitterer¹, Joerg Latus¹, Wolfgang Steurer³, Peter Fritz¹, Angela Geissler¹, M. Dominik Alschel¹, Stefan Sagerer², Christoph Ulmer¹, Niko Braun¹
¹Department of Internal Medicine, Division of Nephrology, Robert-Bosch-Hospital, Stuttgart, Germany; ²Department of General, Visceral and Trauma Surgery, Robert-Bosch-Hospital, Stuttgart, Germany; ³Department of Radiology and Nuclear Medicine, Robert-Bosch-Hospital, Stuttgart, Germany; ⁴Division of Pathology, Robert-Bosch-Hospital, Stuttgart, Germany; ⁵Department of Pathology, University Hospital, Zurich, Switzerland; ⁶Division of General Internal Medicine and Nephrology, Robert-Bosch-Hospital, Stuttgart, Germany

Background: The diagnostic pillars of encapsulating peritoneal sclerosis (EPS) are based on clinical symptoms, radiologic findings, macroscopic and histological criteria. Two diagnostic scores for radiologic findings in CT scans of EPS patients have been established in the past (Tarzi et al., Vlijm et al.). Whether these scores resemble different macroscopical phenotypes, leading to specific surgical techniques with different patient outcome has not been investigated yet.

Methods: We retrospectively analyzed 30 late-stage EPS patients of our referral center who underwent major surgery with perit昂otomy and enterolysis (PEEL). The preoperative CT scans scored according to the two established systems. The macroscopic phenotype, the surgical procedure and laboratory values at the time of surgery were noted. Correlations were studied between CT findings and the macroscopic phenotype.

Results: Using both scoring systems, all patients had highly predictive CT-scores for EPS. The macroscopical Type III had significantly higher C-reactive protein (CRP) values compared to EPS Type I. Calcifications were detected in 11 out of 15 in Type III and in 2 out of 9 in Type I (p <0.05). Operation time was significantly longer, requirement for redo surgery was higher (p <0.05) and intraoperative complications were more frequent in EPS Type III compared to EPS Type I (p <0.001).

Conclusions: Higher scores were associated with bowel obstruction due to intestinal cocooning. Surgical treatment of EPS Type I is associated with more intraoperative complications and longer operation time requiring different surgical techniques. The combination of CT scores, CRP levels, calcifications and absence of fluid loculation might be a useful tool to separate Type I from Type III. This differentiation is important to plan a proper operation procedure and might influence a decision in favor or against initiation of a medical therapy.

Validation of a specific screening score for sleep disordered breathing in patients undergoing chronic intermittent hemodialysis

Valentina Forni Ogna¹*, Adam Ogna², Menno Pruijim¹, Isabelle Bassi¹, Georges Halabi¹, Thierry Gauthier¹, Roberto Bullani¹, Olivier Phar¹, Anne Cheripold³, Claudiine Mathieu¹, Daniel Teta¹, Alexandra Mihalache³, Michel Burnier¹, Raphaël Heinzer¹
¹Service of Nephrology and Hypertension, University Hospital and University of Lausanne (CHUV), Lausanne, Switzerland; ²Center for Investigation and Research in Sleep (CIRS), University Hospital of Lausanne (CHUV), Lausanne, Switzerland; ³Etablissements Hospitaliers du Nord Vaudois, Yverdon, Switzerland; ⁴Hemodialysis Unit, Hôpital Riviera Site de la Providence, Vevey, Switzerland; ⁵Hemodialysis Unit, Hôpital de Morges, Morges, Switzerland; ⁶Hemodialysis Unit, Hôpital Intercantonal de la Broye, Payerne, Switzerland; ⁷Hemodialysis Unit, Hirslanden Clinique Ceci, Lausanne, Switzerland; ⁸Valentina Forni Ogna and Adam Ogna: Joint First Authorship

Introduction: We previously described a 56% prevalence of sleep disordered breathing (SDB; including obstructive and central sleep apnea) in hemodialysis (HD) patients, which was under-diagnosed and undertreated. The best diagnostic approach currently is undefined, since no screening tool has been validated in this population. We aimed to evaluate the performance of classical screening scores for SDB and to propose a new specific screening score.

---

Oral communications – Dialysis

OC 21

Oral communications – Hypertension / Mineral / Electrolytes

OC 20
Methods: 104 patients from 6 HD centers in Canton Vaud were assessed by home polygraphy to measure the apneas-hypopneas index (AHI) and completed 3 SDB screening scores: STOP-BANG, Berlin’s Questionnaire (BQ) and Adjusted Neck Circumference (ANC). The patients were divided in a derivation and an independent validation population, according to the HD-center. Multivariate logistic regression and CART-analysis were used to identify the best predictors of SDB and develop the new score.

Results: Classical screening tools were not reliable for SDB screening in HD patients with a sensitivity/specificity of 52/54% for BQ, 85/54% for STOP-BANG and 30/91% for ANC respectively. Age, neck circumference and time on renal replacement therapy were identified as the best predictors of moderate to severe SDB in the derivation population and were used to develop a new screening score, specific to the HD population: the ANT (age-neck-time)-score. The herein proposed ANT-score showed 90% [82–99] sensitivity and 64% [49–78] specificity in the validation population. On ROC-analysis, the ANT-score (ROC-area 0.845 [SE 0.066]) performed better than the 3 classical scores in the validation population (ROC-areas 0.538 [0.093] for BQ, 0.652 [0.085] for STOP-BANG and 0.655 [0.083] for ANC).

Conclusion: Classical screening scores showed poor performance for SDB screening in HD patients. We therefore propose a simple screening score specific to the HD population, based on readily available clinical data (the ANT-score), to identify the patients who need further investigation. This score needs to be validated prospectively.

Calcitriol concentrations increase significantly in patients on maintenance hemodialysis (HD) receiving long-term cholecalciferol supplementation

Eric Descombes1, Benoît Fellay2, Yann Guillod2, Ould Maouloud Hemett1, Jean-Luc Maginn2, Gilbert Fellay1
1Service of Nephrology, HFR Fribourg Hôpital Cantonal, Fribourg, Switzerland; 2Central Laboratory, HFR Fribourg Hôpital Cantonal, Fribourg, Switzerland; MCL Laboratory, Niederwangen, Switzerland

Background: All HD patients of our center having low baseline vitamin D levels receive cholecalciferol supplementation in order to maintain the 25(OH)D levels within the optimal range of 75–150 nmol/l.

Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal range</th>
<th>Baseline</th>
<th>24 month</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calcium</td>
<td>2.20-2.55 mmol/l</td>
<td>2.32±0.17</td>
<td>2.37±0.16</td>
<td>p&lt; NS</td>
</tr>
<tr>
<td>Ionized calcium</td>
<td>1.12-1.32 mmol/l</td>
<td>1.14±0.09</td>
<td>1.15±0.07</td>
<td>p&lt; NS</td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.90-1.45 mmol/l</td>
<td>1.55±0.39</td>
<td>1.68±0.49</td>
<td>p&lt; NS</td>
</tr>
<tr>
<td>i-PTH</td>
<td>15-65 ng/l</td>
<td>241±174</td>
<td>311±204</td>
<td>p&lt; NS</td>
</tr>
<tr>
<td>25-OH vitamin D</td>
<td>75-150 nmol/l</td>
<td>32.2±17</td>
<td>109.9±23</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Results are given as mean±SD; * p<0.05 compared to anuric patients; ** p<0.05 compared to non-diabetic patients.

The analysis of our data after 2 years of cholecalciferol supplementation showed an important increase of the calcitriol concentrations and the aim of the present cross-sectional study is to report these long-term results.

Patients and methods: We included all the 35 patients (mean age 69.9 ± 9.5 y; 19 males, 14 diabetics, 1 anephric) who received post-dialysis calcitriol for 2 years. The 25(OH)D and 1,25-DihydroxyVitaminD (calcitriol) levels were measured at baseline and after 24 months. Total 25(OH)D was measured with the COBAS 6000 immunoassay (ROCHE) and calcitriol with aRIA kit (Immudiagnostics system; reader: Wizard gamma Counter, PerkinElmer).

Trice weekly post-dialysis Cefepime prescription in patients on maintenance hemodialysis

Filipe Martins1, Ould Maouloud Hemett1, Veronique Erard2, Christian Chuard1, Eric Descombes2
1Service of Nephrology, HFR Fribourg Hôpital Cantonal, Fribourg, Switzerland; 2Service of Infectious Disease, HFR Fribourg Hôpital Cantonal, Fribourg, Switzerland

Introduction: In chronic hemodialysis patients the post-dialysis prescription of intravenous antibiotics allows to manage even severe infections on an outpatient basis. Cefepime is a 4th generation cephalosporin with a broad spectrum and bactericidal activity in monotherapy. We report here the pharmacokinetic of cefepime after post-dialysis prescription.

Methods: 12 infectious episodes occurring in 9 patients (mean age = 69 ± 7 y) were treated with post-dialysis cefepime. The sites of infection were: lungs (4), urinary tract (3), catheter-related (2), skin, bone and digestive tract. The causal pathogen was identified in seven episodes. The initial post-dialysis dose of cefepime ranged from 750 to 1500 mg and was thereafter adapted according to the through serum levels obtained before the subsequent dialysis in order to be above the breakpoints/MIC90 of susceptible organisms. Cefepime concentrations were determined before (n = 30) and after (n = 17) dialysis by liquid chromatography–mass spectrometry (LC-MS/MS).

Results: The mean ± SD dose of cefepime used was 920 ± 270 mg (14.5 ± 5.1 mg/kg). The mean through pre-dialysis concentrations were 10.7 ± 3.9 mg/l and 11.3 ± 5.6 mg/l at 48 and 72 hours, respectively. These levels always exceeded largely the EUCAST breakpoints for susceptibility of all the targeted bacteria (>1 mg/l), with the exception of Pseudomonas aeruginosa for which the susceptibility breakpoint is higher (>8 mg/l). Pre-dialysis cefepime concentrations were significantly higher in anuric patients compared to those with a conserved diuresis (15.6 ± 3.5 vs 9.25 ± 3.6 mg/l; p < 0.001). The mean post-dialysis cefepime concentration was 1.96 ± 1.17 mg/l. The clinical evolution of all patients was favorable.

Conclusion: Outpatient treatment with cefepime administered post-dialysis proved to be safe and effective in our patients, while reducing hospital stay and improving quality of life. According to our data, the initial dose of cefepime should be 1 g/48 h and 1.5 g/72 h, to be adapted thereafter according to the pre-dialysis through serum levels. Higher doses may be necessary in patients having a residual renal function or with Pseudomonas infection.
Results: After 24 months, the mean dose of the cholecalciferol supplement was 10400 ± 5980 IU/week. The main results are reported in Table 1. Under cholecalciferol supplementation the 25(OH)D3 and the calcium concentrations increased significantly, with 12 out the 35 patients (35%) achieving calcium concentrations within normal range (>43 pmol/l). The calcium concentrations increased by 73% in patients having a conserved diuresis (p <0.05) but only by 31% in the anuric ones (p <0.05) and only slightly in diabetic patients (p = NS).

Conclusions: In patients on maintenance HD the long-term prescription of cholecalciferol is associated to a significant increase of the calcitriol levels – particularly in non-diabetic patients – suggesting the persistence of a 1-alfa hydroxylation activity. The higher increase observed in patients with conserved diuresis supports renal synthesis; however extrarenal synthesis may be present as well, as also suggested by the calcitriol levels observed in anephric HD patients. Overall, our data suggest that the calcitriol deficiency developing with progressive CKD may be partly due to vitamin D deficiency and thus could be partially corrected or prevented by cholecalciferol supplementation.

Implementation of nutritional risk screening in daily clinical routine and evaluation of clinical outcome in a tertiary nephrology department
Spyridon Arampatzis1, Vasileios Devetzi1, Susanne Gerber1, Sibylle Eicken1, Bruno Vogt1, Uyen Huynh-De1
1Department of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Bern University Hospital, Bern, Switzerland

Background: Malnutrition is a debilitating condition among chronic kidney disease (CKD) patients, associated with protein-energy wasting and increased need for medical resources and adverse outcomes. However nutritional screening upon hospital admission is infrequently performed in nephrological wards. The aim of the present study was to evaluate the implementation of a nutritional risk screening in daily routine medical care and to explore the impact of malnutrition on the clinical outcome of CKD patients.

Methods: We screened all admissions (n = 747) between January and December 2013 at our nephrology department for malnutrition according to the Nutrition Risk Screening 2002 (Sorensen). Cases with a score of 3 or more, which denotes severe malnutrition or patient “at risk” for malnutrition were analyzed.

Results: Out of 747 admissions, 35% were defined as ‘at-risk’. ‘At-risk’ admissions requiring nutritional support (18 ± 18 vs. 6 ± 6 cases, P <0.001) and caused higher treatment costs (41178 ± 47158 vs. 14123 ± 14188 CHF, P <0.001), than ‘not at-risk’ patients. After adjusting for several confounders (age, gender, comorbidities, length of hospitalization, readmissions and AKIN stage) multivariate analysis confirmed an independent and significant association between higher in-hospital mortality and NRS ≥3 [OR 1.82 (1.30–2.56), P <0.001] along with functional status assessed by Barthel-Index [OR 3.66 (1.03–13.02), P <0.05].

Conclusion: Malnutrition is evident in up to one third of the admissions and is associated with increased cost, length of stay and in-hospital mortality. Our results underscore the need to establish a routine screening and therapeutic nutritional follow-up in CKD patients.

FGF-23 or PTH: which comes first in CKD?
Hans Freudiger
Dialysis unit, Onex-Geneva

Background: Control of Calcium-Phosphate (Ca-Pi) metabolism represents a good part of a nephrologist’s workload. Despite considerable progress in understanding, diagnosing and treating Ca-Pi related problems in patients with chronic kidney disease (CKD), Ca-Pi remain one of the leading risk factors responsible for the excess mortality rate in CKD-patients. This may be due to the complexity of this multormonal system, where correcting one parameter may trigger considerable rhematological changes.

Aim of the study: To evaluate the complexity of a multifactorial system with respect to its importance and chronology of its appearance.

Patients, material, methods: Cosssectional, single center. New patients consulting the first time during 2012 were enrolled (n:54), as well as all patients on HD (36). CaPi + FGF-23, PTHi, VitD were measured.

Results: This study clearly reveals FGF-23 to be the first factor to rise with doubling of blood levels in CKD-3 (10/11 pts showed high blood levels), whilst PTHi (2/8pts high), Pi (1/8) and VitD (1/8) displayed pathological values only as CKD progressed to CKD-4. This study also shows that chronic renal insufficiency of moderate degree (<CKD-3) is not associated with any measurable significant alterations in kidney functions other than increase of creatinine. As progression of CKD continues and reaches CK-5 FGF-23 displays in some pts values 1000 times the upper norm. On HD FGF-23 level is negatively influenced by the level of vitaminD.

Conclusions: This study gives some more evidence that in chronic renal insufficiency, FGF-23 is the first factor to react on a change in CaPi handling, and suggest the importance of this reaction to be dependent of the status of vitaminD. All this adds to the fact of the importance of individualisation of the treatment of hyperPi, therefore protection of ectopic calcifications. FGF-23 should be included in a regularly CaPi-work-up.
Hypertension, kidney function and proteinuria were selected as criteria for long-term outcome.  

Results: Prominent clinical findings during acute NE were fever (90%), back pain (67%), limb pain (71%) and nausea and vomiting (47%). In total 88% of the patients had detectable Hantavirus-specific IgG; 8.5% had persistent IgM antibodies; 25% had hematuria; 23% had hypertension (33% pre-existing and 67% newly diagnosed); 7% had proteinuria.

Conclusions: NE causes AKI in a high proportion of patients. Hypertension and proteinuria do not seem to be long-term consequences of NE, whereas Hematuria might be. All patients had Hantavirus-specific IgG antibodies years after the infection.

New anthropometry-based age- and sex-specific reference values of the urinary 24-h creatinine excretion based on the adult Swiss population

Valentina Forni Ogna1, Adam Ogna2, Menno Pronk2, Philippe Vuistin1, Belen Ponte1, Daniel Ackermann1, Luca Gabutti1, Nima Vakilzadeh1, Markus Mohaupt1, Pierre-Yves Martin1, Idriss Guessous2, Antoinette Pechère-Bertschi2, Frédéric Pascal1, Murielle Bochud2, Michel Burnier1, On Behalf Of The Swiss Survey On Salt Group

1Service of Nephrology and Hypertension, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; 2Department of Internal Medicine and Nephrology, Regional Hospital, Locarno, Switzerland; 3Service of Nephrology and Hypertension, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; 4Community Prevention Unit, University Institute of Social and Preventive Medicine (IUMSP), Lausanne, Switzerland; 5Clinic for Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland; 6Service of Nephrology, Department of Specialties, University Hospital of Geneva, Geneva, Switzerland; 7Unit of Population Epidemiology, Geneva University Hospitals, Geneva, Switzerland; 8Department of Community Medicine and Primary Care and Emergency Medicine, University Hospital of Geneva, Geneva, Switzerland; 9The Swiss Survey On Salt Group (Conen D. (Basel), Hayoz D. (Fribourg), Erne P. (Luzern), Binet I. (St-Gallen), Muggli T. (Ticino), Galliano A. (Ticino) and Suter P.M. (Zürich); 10Valentina Forni Ogna and Adam Ogna: Joint First Authorship; 11Murielle Bochud And Michel Burnier: Joint Last Authorship

Background: Urinary creatinine excretion is used as a marker of the completeness of timed urine collections. The current reference values for 24-h urinary creatinine excretion are poorly representative of the general European population.

The aim of this study was to establish and validate anthropometry-based age- and sex-specific reference values of the urinary 24-h creatinine excretion on two independent adult populations.  

Methods: We used data from two independent Swiss cross-sectional population-based studies with standardized 24-h urine collection and measured anthropometric variables. Only data from adults of European descent, with estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m² and reported completeness of the urinary collection were retained. A prediction model for the completeness of 24-h urinary creatinine excretion was developed in 1137 participants from the Swiss Survey on Salt (SSS) and validated in 994 participants from the Swiss Kidney Project on Genes in Hypertension (SKIPoGH).

Results: The mean urinary creatinine excretion was 193 ± 41 µmol/kg/24 h in men and 151 ± 38 µmol/kg/24 h in women in SSS. The values were inversely correlated with age and body mass index (BMI). Based on current reference values (177–221 µmol/kg/24h in men and 133–177 µmol/kg/24 h in women), 56% of the urinary collections in the whole population and 67% in subjects >60 years would have been considered as inaccurate.

A linear regression model with sex, BMI and age as predictor variables was found to provide the best prediction of the observed values.

Conclusions: We propose a validated prediction equation for 24-h urinary creatinine excretion in a general Swiss population, based on readily available variables such as sex, BMI and age, and few derived normograms to ease its clinical application. This should help healthcare providers to interpret the completeness of a 24-h urine collection in the daily clinical practice and in epidemiological population studies.

Primary antiphospholipid syndrome presenting as renal vein thrombosis and membranous nephropathy

Katrin König1, Caroline Wehmeier1, Helmut Hopfer2, Theresia Klima2, Min Jeong Kim3

1Clinic for Transplant Immunology and Nephrology, University Hospital Basel; 2Institute for Pathology, University Hospital Basel; 3Institute for Pathology, University Hospital Basel

Background: Antiphospholipid syndrome (APS) is a multisystem autoimmune disorder characterized by thrombotic events and/or recurrent pregnancy complications in the presence of circulating antiphospholipid antibodies (APL). APS may be primary or associated with other autoimmune disease. Commonly described renal findings are major vessel thrombosis, renal artery stenosis and thrombotic microangiopathy. Non-thrombotic glomerulonephritis are however increasingly recognized in patients with primary APS.

Case report: We report a case of a 26-year-old female who presented with left flank pain for a few weeks. Medical history and physical examination were otherwise unremarkable. Initial laboratory examination revealed increased serum creatinine (138 µmol/L) and LDH (602 U/l), hypoalbuminemia (16 g/l) and mild proteinuria (spot urine protein-creatinine ratio 51 mg/mmol). Further evaluation showed complete obliteration of the left renal vein (MRI) and positive APL in the absence of other autoimmune disorders or malignancy, which led to the diagnosis of primary APS (PAPS). Persistent positive APL 3 months later confirmed the diagnosis. During the hospitalisation, she developed a nephrotic syndrome with edema and heavy proteinuria (5 g/d). A 99mTc-MAG3-sciography revealed a non-functioning left kidney. Due to the persistent nephrotic syndrome despite anticoagulation and antithrombotic therapy for 3 months, a biopsy of the single functioning kidney was performed, which revealed membranous nephropathy stage 3. Given the persistent nephrotic syndrome and impaired renal function, prednisone and tacrolimus were added to the therapy regimen.

Conclusion: Recently, non-thrombotic glomerulopathies in association with PAPS, in particular membranous nephropathy have been reported. The pathogenic role of APL in the causation of
glomerular disease in general and in membranous nephropathy is not clear. Our report highlights the impact of circumventing APL on the kidney of a previously healthy young female and illustrates a rare potential clinical presentation ofAPS.

The changing pattern of postinfectious glomerulonephritis
Andreas Fischer1, Walter Arnold2, Helmut Hopfer1
1Nephrology, Kantonsspital LUZ KUznern; 2Pathologisches Institut, LUZ Luzern; 3Institut für Pathologie, Universitätsspital Basel

Background: The classical form of poststreptococcal disease is decreasing worldwide but remains a significant health care problem in developing countries, especially in children. In industrialised countries postinfectious glomerulonephritis is now primarily due to non-streptococcal disease and affects elderly patients.

Case report: A 71 year old patient with diabetic foot syndrome presented with severe renal failure, nephritic uranalysis and signs of inflammation (CRP 407 g/l). Complement C3 and C4 were normal. Urine culture was positive for methicillin-sensitive staphylococcus aureus. Despite adequate antibiotic therapy renal function worsened and haemodialysis was started. Renal biopsy showed a mesangiproliferative and endocapillary glomerulonephritis with concomitant acute tubular injury and chronic lesions due to beginning diabetic nephropathy. Subepithelial humps were demonstrated on electron microscopy. Screening for endocarditis was negative. One week after cessation of flucloxacillin lower back pain developed and recurrence of the inflammatory syndrome was observed. Blood cultures were positive for staphylococcus aureus. An acute aortic syndrome with aortic dissection and a high metabolic workload in children with one kidney.

Renal tissue oxygenation as measured with BOLD-MRI in children with vesico-ureteral reflux or a solitary kidney in comparison with healthy controls
Hassib Chehade1, Maciej Piskunowicz2, Bastien Milan3, Isabelle Bassi1, Christiane Anex1, Matthias Stuber1, Bruno Vogt1, Michel Burnier1, Monno Pruym1
1Nephrology, University Hospital Lausanne CHUV; 2Radiology, University Hospital Gdansk; 3Radiology, University Hospital Lausanne CHUV; 4Department of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Bern University Hospital, Department of Clinical Research, University of Bern, Switzerland

Background: Vesico-ureteral reflux (VUR) in children is a risk factor for the development of renal scarring and chronic kidney disease (CKD), yet the underlying pathophysiology is incompletely understood. Renal hypoxia might be one of the underlying mechanisms contributing to the progression of CKD in these children, yet this has not been assessed so far. We measured cortical and medullary oxygenation in children with VUR, SK or UN, and compared the results with those of healthy controls using blood oxygen level dependent magnetic resonance imaging (BOLD-MRI).

<table>
<thead>
<tr>
<th>Reflux</th>
<th>Solitary Kidney</th>
<th>Unilateral Nephrectomy</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of patients</td>
<td>18</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>15.7±1.4</td>
<td>14.4±1.0</td>
<td>16.5±1.1</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>66.7</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>eGFR quadratic formula (ml/min/1.73m2)</td>
<td>88±14</td>
<td>96±9</td>
<td>85±2</td>
</tr>
</tbody>
</table>

Methods: BOLD-MRI was performed under standardized hydration conditions, before and after the administration of furosemide. Four coronal slices were selected in each kidney, and combination sequence was used to acquire T2* weighted images. The mean R2* values (=1/T2*) were calculated for each kidney, a low R2* indicating a high tissue oxygenation.

Results: A total of 51 children (26 controls and 25 patients) participated in the study, corresponding to 95 kidneys. Baseline characteristics and results of MR-measurements are shown in the table. In all groups, cortical oxygenation was higher (R2* lower) in girls than in boys. Medullary and cortical R2* levels were significantly higher (p = 0.003 and 0.02 respectively) and medullary R2* decreased more under stimulated conditions (furosemide injection) in healthy controls than in reflux kidneys (p = 0.02). The highest medullary R2* values and furosemide-induced decreases were seen in the UN and SK groups.

Conclusion: These data suggest that VUR is not associated with chronic hypoxia in children. The large furosemide-induced decreases in medullary R2* levels in the solitary kidney- and unilateral nephrectomy- groups point towards intense renal sodium transport and a high metabolic workload in children with one kidney.

Should we care about the sequelae of preeclampsia?
Michael Girsberger1, Catherine Wiesner2, Irene Hösl3, Michael Dickemann4
1Nephrology, Kantonsspital Basel, Liestal; 2Department of Obstetrics and Gynecology, University of Basel, Switzerland; 3Transplantation Immunology and Nephrology, University Hospital Basel, Basel, Switzerland

Background: Preeclampsia is characterized by the onset of hypertension and either proteinuria or organ dysfunction after 20 weeks of gestation. Epidemiological data on sequelae in the first year after preeclampsia are scarce. We investigated kidney function, hypertension, proteinuria and urine sediment in women with preeclampsia six month after delivery.

Methods: From January 2007 to July 2014 women with preeclampsia and 6-months follow up at the university hospital Basel were analyzed. Hypertension was defined as a blood pressure ≥140/90 or the use of antihypertensive medication. Proteinuria was defined as a protein-to-creatinine ratio in a spot urine >11.0 mg/mmol. Urine sediment was evaluated by a nephrologist.

Results: 202 women were included into the analysis. The mean time of the follow up visit was 172 days (±39.6) after delivery. Mean age of the 202 women was 32 years (±5.9). The mean blood pressure at follow up was 124/76 mm Hg (±14/11, range 116-182/63-110) and the
mean serum-creatinine was 61.8 μmol/l (± 11.6). Mean estimated glomerular filtration rate using CKD-EPI was 110.7 mmol/min/1.73 m² (range 59.7–142.4 mmol/min/1.73 m²). 20.3% (n = 41) had a blood pressure of 140/90 or higher (mean 143/89 mm Hg) or were receiving antihypertensive medication (5.5%, n = 11). Proteinuria was present in 33.1% (n = 66) (mean 27.5 mg/mmol, range 12–261 mg/mmol). Proteinuria and hypertension was present in 8% (n = 16). No active urine sediment (e.g. signs of glomerulonephritis) was observed.

**Conclusion:** Hypertension and proteinuria are frequent in women 6-months after preeclampsia and delivery. The findings stress the importance of a close follow up to identify those women who need further care.

---

**Screening for sleep disordered breathing in ESRD patients scheduled for renal transplantation**

Adam Ogna*, Valentina Forni Ogna*, José Haba Rubio†, Nadia Tobbacman, Isabella Basseti*, Jean Pierre Venetz†, Delazyl Golshayan†, Ghaith Nseir†, Maurice Matter†, Manuel Pascualy, Raphael Heinzer‡, Center for Investigation and Research in Sleep (CIRS), University Hospital of Lausanne (CHUV), Lausanne, Switzerland; †Service of Nephrology and Hypertension, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; ‡Center for Organ Transplantation (CTO), University Hospital of Lausanne (CHUV), Lausanne, Switzerland; *Valentina Forni Ogna and Adam Ogna: Joint First Authorship

**Rationale:** Sleep disordered breathing (SDB) is a common finding in end stage renal disease patients and represents a risk factor for perioperative complications. The prevalence of SDB in the patients on waiting list for renal transplantation is poorly described and there are no guidelines about its screening before transplantation surgery. Our aim was to assess the prevalence of SDB in a Swiss HD population and to evaluate the predictive value of classical screening scores.

**Methods:** Patients on the Lausanne renal transplantation's waiting list were screened for SDB using home nocturnal polysomnography to measure the Index of Apnea-Hypopneas per hour of sleep (IAH). Participants also completed 3 SDB screening scores: STOP-BANG questionnaire, Berlin's Questionnaire (BQ) and Adjusted Neck Circumference (ANC).

**Results:** 44 men and 16 women were assessed; mean age was 55.5 (±1.5) years and mean BMI 26.8 (±4.2) kg/m². 68% were on hemodialysis, 11% on peritoneal dialysis and 17% had no renal replacement therapy. 76% of the participants had a SDB (IAH >5): 30% had mild (IAH 5–15), 18% moderate (IAH 15–30) and 30% severe SDB (IAH ≥30). SBD had been previously diagnosed in 11% of patients and was treated in 5%. Positive (PPV) and negative predictive values (NPV) for moderate to severe SDB were 55% and 64% respectively for BQ, 63%/64% for STOP-BANG and 60%/65% for ANC.

**Conclusion:** We observed a high prevalence of SDB among patients on waiting list for renal transplantation, which is largely underdiagnosed and untreated. Classical screening scores do not seem to be reliable to screen for SDB in this population. Given the increased perioperative complication risk associated with SDB, the implementation of SDB screening using home sleep recordings in the pre-operatory assessment of renal transplantation candidates should be considered.

**Acknowledgements:** This study was supported by grants of the Schweizerische Nierenstiftung and the Ligue Pulmonaire Vaudoise.
extraluminal in the electrophoresis of a patient with ARF caused by penicillin-overdosing
Stefan Kalbematter¹, Thomas Menter², Helmut Hopfer¹, Carmen Volkert¹, Denes Kiss¹
¹Nephrology, Kantonsspital Baselland, Liestal; ²Laboratory Medicine, Kantonsspital Baselland

History: (Background) A 86-year-old man with a history of back pain and fever (39.0 °C), was referred to our hospital. The MRI of the lumbar spine was suspicious for a spondylodiscitis. In the blood cultures staphylococcus aureus could be detected. An intravenous treatment with penicillin (3x5 million units/day) was started. After ten days of treatment the serum creatinine started to increase continuously.

Clinical Examination and Laboratory Examination: (Methods) After four weeks of treatment the patient was free of pain and afebrile but became progressively weak – heart rate 76 bpm and RR 170/80 mm Hg. C-reactive protein (CRP) was 91 mg/l, s-Cr 437 µmol/l, albumin 29 g/l, haemoglobin 102 g/l; urinary protein-creatinine ratio was 65 mg/96 ml/min/1.73 m². The urinary protein-creatinine ratio was 65 mg/96 ml/min/1.73 m². Renal biopsy revealed a heavy acute eosinophilic interstitial nephritis.

Course: (Results) After stopping the penicillin treatment (3x5 million units/day) was started. After ten days of treatment the patient was free of pain and afebrile but became progressively weak – heart rate 76 bpm and RR 170/80 mm Hg. C-reactive protein (CRP) was 91 mg/l, s-Cr 437 µmol/l, albumin 29 g/l, haemoglobin 102 g/l; urinary protein-creatinine ratio was 65 mg/96 ml/min/1.73 m². Renal biopsy revealed a heavy acute eosinophilic interstitial nephritis.

Conclusion: (Conclusion) The phenomenon of reflex anuria as a rare cause of abrupt anuric renal failure has been described in the literature for decades. Spasms of intrarenal arterioles as well as ureters in both kidneys by the activation of sympathetic nervous system in response to irritation or trauma to one kidney or ureter, or severely painful stimuli to other organs were postulated as underlying mechanism of reflex anuria. Here we report 4 cases of acute anuric renal failure secondary to reflex anuria at the University Hospital Basel between September 2013 and September 2014.

Case report: 4 cases are summarized in the table.

Conclusion: Our 4 cases of reflex anuria identified within a period of 12 months underline that reflex anuria is not as rare as previously suggested in the literature, and should be considered as diagnosis of exclusion in case of acute anuric renal failure. With respect to the advanced age of the patients reported, reflex anuria might be an increasing phenomenon in elderly patients with polymorbidity as a result of dysfunctional autonomic nervous system.
during several years sometimes of multiple organ metastatic localizations except pancreatic of the primary tumor with heavy treatments and their consequences, sometimes a multiple myeloma unconfirmed by marrow biopsies but treated as such, until the worsening radiological images and the biopsy of solitary right kidney who raises the diagnosis of IgG4-RKD.

Hapto Tc WBC 58 3.5 82 eGFR Schistoc <0.15 58 3295 12 85 5883 Reti Vit B12 126 <0.15 <50 18

pancytopenia. Kidney function was normal and urine analysis

Initial laboratory results showed severe schistocyte positive exertion. She had no paraesthesia or other neurological symptoms.

First patient is a 37-year-old female from Sri Lanka with a two weeks deficiency in young patients mimicking TMA.

literature and in practice often misdiagnosed whereas aggressive including plasma exchange. Rarely in severe cobalamine deficiency mortality. The classic treatment includes aggressive therapies Kantonsspital St. Gallen Christian Bucher

microangiopathy – a sheep in wolf’s clothing?

Severe cobalamine deficiency mimicking thrombotic microangiopathy – a sheep in wolf’s clothing? Christian Bucher1, Carola Epp2, Isabelle Binet1

1Klinik für Nephrologie und Transplantationsmedizin, Kantonsspital St. Gallen; 2Klinik für Allgemeine Innere Medizin/Hausarztmedizin, Kantonsspital St. Gallen

Thrombotic microangiopathy (TMA) carries a high morbidity and mortality. The classic treatment includes aggressive therapies including plasma exchange. Rarely in severe cobalamine deficiency pseudo-TMA is found. This condition is not well described in the literature and in practice often misdiagnosed whereas aggressive PEX is not indicated. We report two cases of severe cobalamine deficiency in young patients mimicking TMA.

First patient is a 37-year-old female from Sri Lanka with a two weeks history of fatigue, mild headache, epigastric pain and dyspnoea on exertion. She had no paraesthesia or other neurological symptoms. Initial laboratory results showed severe schistocyte positive pancytopenia. Kidney function was normal and urine analysis unremarkable. Detailed findings are given in the table below. Based on the findings of severe Coombs negative haemolysis and thrombocytopenia immediately daily plasma exchange and steroids were started. After receiving serum cobalamin result <50 pg/ml and search of the literature the TMA-treatment was stopped in absence of neurological and renal symptoms. Homocysteine level (35 µmol/l) consistently remained <5% in all subsequent plasma samples. No ADAMTS13 inhibitor was detected at any time. Prior to transplantation, thrombocytopenia or hemolysis had never been observed. After diagnosing arterial hypertension at age 33, CKD3A with proteinuria of ~1 g/dl was found at 38y. His GFR decreased at ~3 ml/min/year. Kidney biopsy at GFR of 20 ml/min was nonspecific. At 49 y he developed homonymous hemianopia due to cerebral ischemia. At 56 y, he was preemptively transplanted with a deceased donor kidney. There were two episodes of mild thrombocytopenia without hemolysis in the first month. Four transplant biopsies, one at the time of the plasmapheresis, showed no evidence of thrombotic microangiopathy.

The laboratory findings made congenital ADAMTS13 deficiency a plausible diagnosis, which is due to homozygote or compound heterozygote mutations in the ADAMTS13 gene. In our case, sequence analysis revealed a mutation (p.R1060W) in one allele, further studies are pending.

Conclusion: Severe deficiency of ADAMTS13 activity may remain silent for decades, until other factors trigger clinical TTP. Retrospectively, hypertension, renal disease and the cerebrovascular incident in this patient may have been manifestations of TTP. Congenital ADAMTS13 deficiency may explain some cases of renal failure in cryptogenic CKD, and should be liberally treated with FFP when renal function deteriorates for unknown reasons.

<table>
<thead>
<tr>
<th>Hb (g/l)</th>
<th>WBC (G/l)</th>
<th>Tc (G/l)</th>
<th>Reti (%)</th>
<th>Schistoc (%)</th>
<th>LDH (U/l)</th>
<th>Hapto (g/l)</th>
<th>eGFR (CKD-EPI)</th>
<th>VIt B12 (ng/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>58</td>
<td>3.6</td>
<td>61</td>
<td>16</td>
<td>12</td>
<td>5883</td>
<td>&lt;0.15</td>
<td>116</td>
</tr>
<tr>
<td>Case 2</td>
<td>82</td>
<td>3.5</td>
<td>85</td>
<td>18</td>
<td>20</td>
<td>3295</td>
<td>&lt;0.15</td>
<td>126</td>
</tr>
</tbody>
</table>

Living without ADAMTS13: Hereditary TTP in a 56-year-old kidney transplant recipient

Florian Buchkremer1, Corinne Eschler2, Johanna Kremer Hovinga3, Andreas Bock1

1Nephrologie, Kantonsspital Aarau AG; 2Hämatologie, Inselspital Bern; 3Nephrologie, Kantonsspital Aarau AG

Background: Hereditary TTP (Upshaw-Schullman syndrome) is characterized by the congenital absence of ADAMTS13 activity without an inhibitory autoantibody. Kidney involvement occurs in up to 10% of patients, and ESRD – unlike in acquired TTP- has been frequently described.

Case report: Seven months after kidney transplantation, a 56 yo patient presented with nosebleeds and soft tissue hematomas. Workup revealed mild microangiopathic hemolytic anemia and thrombocytopenia. Plasma ADAMTS13 activity of <5% of normal confirmed a diagnosis of TTP Plasmapheresis with FFP replacement led to clinical resolution within 1 week. No evidence of TTP was detectable throughout the following year, although ADAMTS13 activity consistently remained <5% in all subsequent plasma samples. No ADAMTS13 inhibitor was detected at any time. Prior to transplantation, thrombocytopenia or hemolysis had never been observed. After diagnosing arterial hypertension at age 33, CKD3A with proteinuria of ~1 g/dl was found at 38y. His GFR decreased at ~3 ml/min/year. Kidney biopsy at GFR of 20 ml/min was nonspecific. At 49 y he developed homonymous hemianopia due to cerebral ischemia. At 56 y, he was preemptively transplanted with a deceased donor kidney. There were two episodes of mild thrombocytopenia without hemolysis in the first month. Four transplant biopsies, one at the time of the plasmapheresis, showed no evidence of thrombotic microangiopathy.

The laboratory findings made congenital ADAMTS13 deficiency a plausible diagnosis, which is due to homozygote or compound heterozygote mutations in the ADAMTS13 gene. In our case, sequence analysis revealed a mutation (p.R1060W) in one allele, further studies are pending.

Conclusion: Severe deficiency of ADAMTS13 activity may remain silent for decades, until other factors trigger clinical TTP. Retrospectively, hypertension, renal disease and the cerebrovascular incident in this patient may have been manifestations of TTP. Congenital ADAMTS13 deficiency may explain some cases of renal failure in cryptogenic CKD, and should be liberally treated with FFP when renal function deteriorates for unknown reasons.
Progressive renal failure after resection of a neuroendocrine tumor of the small intestine

Michael Girberger1, Stefan Kalbmeretter1, Thomas Menter1, Helmut Hopfer1, Denes Kiss1
1Neurologie, Kantonsspital Basel, Liestal; 2Pathology University of Basel

A 70-year old man was referred to our clinic with a history of recurring nephrolithiasis, renal insufficiency and metastatic neuroendocrine cancer of the small intestine. The patient was suffering of diarrhea, night sweats and flushing for 1.5 years before being diagnosed with a neuroendocrine tumor of the small intestine and metastatic liver disease by computer-tomography during evaluation of an episode of urolithiasis. After 145 cm ileocoecal resection of the tumor recurrent nephrolithiasis with urinary tract obstruction and renal insufficiency occurred.

On examination the patient was afebrile, the blood pressure 129/80 mm Hg and the pulses 78 bpm, S-Creatinine was 181 umol/l with an estimated glomerular filtration rate (GFR) of 34 ml/min/1.73 m² (MDRD), S-Calcium 2.27 mmol/l, albumin 38 g/l, uric acid 469 umol/l and haemoglobin 144 g/l. 24-hour urine collection revealed heavy hyperoxaluria (2.89 mmol/24h). Renal biopsy showed acute tubular injury with moderate oxalosis and nephrocalcinosis (picture).

We diagnosed nephrocalcinosis due to heavy hyperoxaluria after short bowel resection with short bowel syndrome. Acute tubular injury was assumed consecutive to recurring urinary tract obstruction. We initiated a treatment of colestyramin, calciumcitrat and pankreatin which can be very effective on oxalate absorption and renal function.

We estimated glomerular filtration rate (GFR) of 34 ml/min/1.73 m². The increase in oxalate absorption is due to binding of free calcium to small molecules such as oxalate induced by exposure of the colon to nonabsorbed bile salts. The treatment with calciumcitrate proved to exceed production, malabsorption of bile acids causes excessive absorption of oxalate, leading to hyperoxaluria and kidney stone formation. The increase in oxalate absorption is due to binding of free calcium to fatty acids in the intestinal lumen and to increased colonic permeability to small molecules such as oxalate induced by exposure of the colon to nonabsorbed bile salts. The treatment with calciumcitrate proved to be very effective on oxalate absorption and renal function.

Simply medullary cystic kidney disease?!

Matthias Zobrist1, Nilafar Mohabbi2
1GZO AG Spital Wetzikon; 2University of Zurich

Case report: A 26-year old caucasian man presented with paraesthesia and cramps parallelized by stupor and hyerventilation. In his medical history he was suffering from chronic kidney disease KDIGO G3b A1 due to medullary cystic kidney disease. Blood chemistry demonstrated hypocalcemia (Calcium ionized 0.98 mmol/l (1.15–1.27)), severe hypomagnesemia (0.38 mmol/l (0.65–1.10)), slight hypophosphatemia (0.7 mmol/l (0.8–1.6)), and an acute respiratory alkalosis (pH 7.53, paCO₂ 2.9kPa, Bicarbonate 17.7 mmol/l). The inactive (25-OH-Vit. D3) and active (1,25-(OH)2-Vit. D3) vitamin D3 levels were in the normal range and the parathyroid hormone was slightly elevated (PTH 11.5 pmol/l (1.5–7.6)) due the impaired kidney function (Creatinine 244 µmol/l (eGFR (CKD-EPI) 30.4 ml/min/1.73 m²)). The physical examination revealed muscle cramps in all extremities with lively reflexes. He received intravenously magnesium, calcium and phosphate and all symptoms disappeared. The combination of medullary cystic kidney disease and severe hypomagnesemia revealed a heterozygous mutation in the Hepatocyte Nuclear Factor-1 Beta (HNF1B) gene.

Discussion: HNF1B is a transcription factor, that is expressed in pancreas, liver, and the kidneys. Mutations lead to an early onset diabetes of the young (MODY, Type 5), neonatal diabetes mellitus or cystic dysplasia of the kidneys and mayoccur as de novo or inherited. The association of renal cysts and diabetes with a HNF1B mutation is termed the renal cysts and diabetes (RCAD) syndrome. Our patient also demonstrated an impaired glucose tolerance (Hba1c 5.6%). The most typical renal manifestation presents as cystic kidney disease. The kidney function depends on the phenotype; 15% of the patients develop ESRD. Hypomagnesemia is caused by impaired magnesium reabsorption in the distal convoluted tubule (DCT). Other organ manifestations such as liver abnormalities, hyperuricemia, and genitourinary tract malformations may also occur.

Conclusion: Chronic kidney disease due to cystic dysplasia combined with hypomagnesemia is indicative of HNF1B mutation. Timely diagnosis and therapy increases quality of life and reduces significantly hospitalisations.
C3 glomerulonephritis in a patient with Down’s syndrome: clinicopathological and genetic findings

Maria Kosmidis1, Albín Schwarz1, Patrice Ambühl1, Ariana Gasperi2
1Institute of Nephrology and Dialysis, Stadtpalast Waid, Zurich, Switzerland; 2Institut für Klinische Pathologie, Universitätsspital Zürich, Switzerland

An 18-year-old male patient with trisomy 21 presented with acute kidney injury and severe hypertension. Urinalysis showed an active sediment with nephrotic proteinuria. Serum complement C3 levels were decreased with normal C4 concentrations. Ultrasound demonstrated renal enlargement with increased parenchymal echogenicity. A kidney biopsy was performed and mesangial matrix increase with hypercellularity as well as thickening of the glomerular basement membrane with double contours were detected.

Immunoﬂuorescence was positive for granular deposits mainly composed of C3 and focal IgA in the glomerular and mesangial compartment, while IgG was absent. Electron microscopy revealed deposits in the mesangium and glomerulus along with microvillar transformation of the podocyte foot processes. Based on these findings C3 glomerulonephritis (C3GN) was diagnosed, a recently described disorder and subtype of C3 glomerulopathy. The disorder affects both genders and all ages [1]. The pathogenesis of glomerular injury in C3GN is supposedly resulting from genetic or acquired dysregulation of the complement system, specifically the alternative pathway. The most common acquired abnormality is the C3 Nephritic Factor autoantibody which stabilizes the C3 convertase with a consequence of complement activation. The genetic defects affect mainly mutations of the genes coding for complement factor H (CFH), complement factor I (CFI) and C3 [2]. In our patient the only finding in genetic analysis and antibody detection by western blot was CFHR3 which frequently occurs in healthy individuals, too. A context finding in genetic analysis and antibody detection by western blot was CFH, complement factor I (CFI) and C3 [2]. In our patient the only finding in genetic analysis and antibody detection by western blot was CFHR3 which frequently occurs in healthy individuals, too.

Dysregulation of the complement system, specifically the alternative pathway is supposed to result from genetic or acquired injury in C3GN. The involvement of toll-like receptor-4 (TLR-4), nuclear factor-kappa B (NF-κB) and NLRP3 pathways. CPP-II induces pro-inflammatory cytokines in response to LTβR signaling. In nephrotic nephritis, the blockade of LTβR signaling reduced crescent formation and parietal epithelial cells responded to LTβR signaling with chemokine release. In a lupus model, LTβR blockade improved renal function without reduction of serum autoantibody titers or glomerular immune complex deposition.

Conclusion: Thus LTβR signaling is involved in renal injury, mediates a new pathway in parietal epithelial cell activation with crescent formation, and is a new therapeutic target in renal diseases.

Calcioprotein particles induce an inflammatory response in macrophages

Prakash Chandra1, Rakesh Bajania1, Edward Smith3, Andreas Pasch4
1Department of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, University of Bern, Bern, Switzerland; 4Department of Nephrology, The Royal Melbourne Hospital, Melbourne, Australia

Introduction: Calcioprotein particles (CPP) are nanoscale mineral-protein aggregates, which have been found in the blood of patients with chronic kidney disease (CKD). These particles contain amorphous (primary CPP) or crystalline (secondary CPP), calcium phosphate along with serum proteins. We investigated whether CPP might induce an inflammatory response in macrophages.

Methods: Prim. and sec. CPP were generated using phosphate- and calcium-enriched cell culture media with varying amounts of FBS. Particles were characterized morphologically by transmission electron microscopy (TEM). Murine RAW-264.7 macrophage-like cells were exposed to increasing amounts of CPP for 24 hrs. RT-PCR was performed to assess interleukin (IL)-6, IL-1β, IL-10, MCP-1, TNF-α and NLRP3. The involvement of toll-like receptor-4 (TLR-4), nuclear factor-kappa B (NF-kB) and NLRP3-dependent pathways were evaluated using selective chemical inhibitors.

Results: TEM imaging of synthetic CPP revealed populations of amorphous spherical (prim. CPP) and larger crystalline spindle-shaped particles (sec. CPP). Exposure of RAW-264.7 cells to sec. CPP resulted in a dose-dependent increase in the expression of pro-inflammatory cytokines (IL-6, IL-1β, MCP-1 and TNF-α). IL-10 expression was unaffected by sec. CPP exposure. In contrast, no inflammatory response was detected upon exposure to prim. CPP. Inhibition of TLR-4, NF-κB and NLRP3 pathways reduced the sec. CPP-induced inflammatory response in RAW-264.7 cells.

Conclusion: Sec. CPP induce pro-inflammatory cytokine expression in the macrophage and this effect may be mediated by activation of TLR-4/NF-κB and NLRP3 pathways. CPP-II might be involved in the induction and maintenance of the chronic inflammatory state commonly encountered in CKD patients.

The Lymphotoxin β receptor is a therapeutic target in renal inflammation

Gitta Seleznek1, Harald Seeger2, Adrian Papandile3, Kai Fu4, Ursjana Poreci5, Julie Czekowicz1, Dania Rabah1, Ann Ranger5, Rakesh J. Anderson1, Maciej Lech6, Rudolf P. Wüthrich1, Nancy H. Rudd1, Marcus J. Moeller7, Jeffrey L. Browning8, Judith Bauer9
1Division of Visceral & Transplantation Surgery, Swiss Hepato-Pancreato-Biliary Center, Zurich, Switzerland; 2Division of Nephrology, University Hospital; 3Switzerland; 4Department of Immunobiology, Biogen Idec, Cambridge, MA, USA; 5Institute of Physiology, University of Zurich, Switzerland; 6Division of Nephrology, Medizinische Klinik und Poliklinik IV, Campus Innenstadt, University of Munich, LMU, Munich, Germany; 7Department of Rheumatology, School of Public Health, Yale University, New Haven, CT, USA; 8Department of Nephrology and Clinical Immunology, Rheinisch-Westfälische Technische Hochschule (RWTH) University Hospital Aachen, Aachen, Germany; 9Department of Microbiology and Section of Rheumatology, Boston University School of Medicine, Boston, MA, USA;

Background: Accumulation of inflammatory cells in different renal compartments is a hallmark of progressive kidney diseases including glomerulonephritis (GN). Follicular infiltrates with defined and organized microarchitecture develop during chronic renal inflammation. Lymphotoxin β receptor (LTβR) signaling is important for the formation of secondary and tertiary lymphoid tissue. Thus we hypothesized that LTβR signaling plays a role in renal inflammation.

Methods: Microarrays from microdissected renal biopsies with lupus nephritis and IgA nephropathy were mined for LTs, LTβR and for NF-κB-regulated genes. The mRNA expression was confirmed by real-time RT-PCR in renal biopsies, and LTβR protein was localized by immunohistochemistry in 36 biopsies from patients with the most common forms of GN. Regulation of LTs and response to LTβR signaling was tested in human mesangial, tubular epithelial cells and mouse parietal epithelial cells in-vitro. LTβR signaling was blocked in two mouse models of GN (nephrotic nephritis and the adenosine A1 receptor agonist accelerated NZB F1 lupus model).

Results: We show that renal biopsies from patients with GN displayed increased levels of LTβ, the ligand for LTβR, mRNA and protein. LTβR was localized to interstitial lymphocytes, and tubular epithelial cells. Human mesangial and tubular epithelial cells expressed both LTα and LTβ RNA upon stimulation with a proinflammatory cytokine in vitro, and expressed chemokines in response to LTβR signaling. In nephrotic nephritis, the blockade of LTβR signaling reduced crescent formation and parietal epithelial cells responded to LTβR signaling with chemokine release. In a lupus model, LTβR blockade improved renal function without reduction of serum autoantibody titers or glomerular immune complex deposition.

Conclusions: Thus LTβR signaling is involved in renal injury, mediates a new pathway in parietal epithelial cell activation with crescent formation, and is a new therapeutic target in renal diseases.

Comparative effects of aliskiren and hydrochlorothiazide on renal tissue oxygenation in patients with arterial hypertension: a BOLD-MRI study

Nima Vakilzadeh1, Menno Pruijm1, Valentina Forni Ogna2, Marie-Eve Muller3, Marc Maillard3, Matthias Stuben3, Lucie Hofmann4, Bruno Vogt4, Michel Burnier5
1Service of Nephrology and Hypertension, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; 2Department of Internal Medicine, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; 3Radiology, University Hospital Lausanne (CHUV); 4Department of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Bern University Hospital, Department of Clinical Research, University of Bern, Switzerland

Background: Animal studies suggest that arterial hypertension is characterized by reduced renal tissue oxygenation and that the latter increases after the acute administration of renin-angiotensin blockers. Since tubular sodium transport is the main determinant of renal tissue oxygenation, our study aimed at comparing the chronic effect of aliskiren versus hydrochlorothiazide (HCT) on renal tissue oxygenation in patients with essential hypertension.

Design and method: This was a single-center, randomized controlled trial. Patients underwent BOLD-MRI (Blood oxygenation level dependent MRI) and renal clearance studies at baseline and 6 weeks after a 25 mg dose of aliskiren (300 mg qd) or HCT (25 mg qd). Four coronal slices were selected in each kidney, and combination sequence was used to acquire T2* weighted images. The mean R2* values (=1/T2*) were calculated, a low R2* indicating a high tissue oxygenation. Response to treatment was defined as a decrease in supine systolic blood pressure (SBP) >10 mm Hg.
Results: 20 hypertensive patients (80% male; age: 53.0 ± 12.3 y) completed the study. Office BP decreased from 147/87 to 142/81 mm Hg in the aliskiren group (n = 11) and from 147/86 to 136/80 mm Hg in the HCT group (n = 9), without significant changes in renal plasma flow or insulin clearance. Plasma aldosterone levels increased significantly in the aliskiren group (p = 0.03). Neither aliskiren nor HCT modified cortical or medullary R2* levels at 6 weeks (see figure). However, BP responders (n = 8) showed a significant decrease in cortical but not medullary R2* levels when compared with non-responders (p = 0.03).

Conclusions: No difference in renal tissue oxygenation as measured with BOLD-MRI was found in patients receiving aliskiren or hydrochlorothiazide for 6 weeks. However, when a decrease of >10 mm Hg occurred in cortical oxygenation occurred, providing new evidence for a beneficial effect of BP reduction on renal oxygenation in hypertensive patients.

ENaC activity in collecting ducts modulates NCC in cirrhotic mice

David Mordinosi1, Dominique Loffing-Cueni2, Johannes Loffing2, Beatrice Rohrbach1, Marc Maillard1, Michel Burnier1, Edith Hummler1, Geneviève Escher1, Bruno Vogt2

1Department of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Bern University Hospital, Department of Clinical Research, University of Bern, Switzerland; 2University of Zurich, Institute of Anatomy, University of Zurich, Zurich, Switzerland; 3Service of Nephrology and Hypertension, CHUV, Rue du Bugnon 17, CH-1005 Lausanne; 4University of Lausanne, Department of Pharmacology and Toxicology, Rue du Bugnon 27

Cirrhosis is a frequent and severe disease, complicated by renal sodium retention with oedema and ascites formation. Although events leading to sodium retention are widely documented, cellular mechanisms unbalancing renal sodium transport are still debated.

The aim of this study was to determine the importance of the amiloride-sensitive sodium channel (ENaC) in collecting ducts, during compensated and decompensated cirrhosis induced by bile duct ligation. We compared control mice (CTL) to collecting ducts specific eNAC knock-out mice (KO).

The disruption of ENaC in cortical collecting ducts did not alter Na,K-ATPase abundance in these segments and did not influence ascites development or plasma aldosterone concentrations. However ENaC in the whole kidney was upregulated in CTL and KO cirrhotic mice. Total eNAC abundance increased, while total eNAC activity did not change in cirrhotic mice of both genotypes. Cleaved forms of α and β ENaC were significantly higher in CTL and KO ascitic mice. Interestingly, the abundance of the αENaC cleaved form was higher in KO ascitic mice than in CTL. The sodium chloride cotransporter protein (NCC) abundance was lower in non ascitic KO, compared to non ascitic CTL mice, but higher in ascitic KO compared to ascitic CTL mice.

Our study demonstrates that in ascitic mice, the lack of ENaC activity in CDs induced an upregulation of NCC and ENaC in upstream segments and modified the cleavage of ENaC subunits, with the presence of ascites. In conclusion, ENaC activity was not a limiting factor for sodium retention, observed in decompensated cirrhosis.

Identification of renal celltype-specific dysregulation of hypoxia-associated transcripts by transcriptome-based network analysis

Natalia Shved1, Gregor Warsow2, David Hoogewijs3, Clemens Cohen1, Maja Lindenmeyer1

1Institute of Physiology, University of Zurich, Zurich, Switzerland; 2University Medicine Greifswald, Greifswald, Germany

Background: The best morphologic indicator of disease progression and development of end-stage renal disease is tubulointerstitial fibrosis and capillary rarefaction. Accumulating evidence suggests that dysregulation of hypoxia-induced transcriptional mechanisms is involved in the loss of renal function and the development of chronic kidney disease (CKD) and hypoxia-induced transcription factors (HIFs) play a role in the dysregulation of gene expression in different renal cell types.

Methods: To study the celltype-specific response to hypoxia and the relevance of HIFs, proximal tubular cells and conditionally immortalized podocytes with stable HIF1α and/or HIF2α suppression were generated. Gene expression analysis of more than 160 renal biopsies from patients with different CKD stages were obtained using Affymetrix arrays. Weighted Correlation Network Analysis (WGCNA) was applied in order to identify modules of genes that showed highly correlated gene expression across cell groups (W). HIF1α, HIF2α, HIF1α+2α and conditions (hypoxia, normoxia). Gene sets from each module underwent GO-enrichment analysis using the topGO library for R, the Pathway System analysis as well as the transcription factor overrepresentation tool from Genomatix.

Results: Microarray analysis of hypoxia-treated renal cells revealed celltype-specific HIF1/HIF2-dependencies as well as dysregulation of several pathways in the renal cell lines. WGCNA analysis resulted in gene sets (modules) that were highly coregulated within the modules. Further characterization of the modules disclosed common as well as cell group- and condition-specific pathways, GO-Terms and transcription factors for each cell line. Expression analysis of hypoxia-associated genes in genome-wide expression profiles revealed correlation of established HIF-target genes with eGFR in cortical tubulointerstitial and glomerular biopsy specimens. These correlations were both positive and negative and in part compartment-specific.

Conclusions: Our gene expression analysis indicates a condition- and celltype-specific dysregulation of hypoxia-associated transcripts in renal cells.
Inhibition of sodium-glucose Cotransporter 2 with Dapagliflozin in Han: SPRD rats with Polycystic Kidney Disease

Daniel Rodríguez, Sanika Kapoor, Ilka Edenhofer, Stephan Seguerer, Melissa Riwanto, Rudolf P. Wüthrich

Department of Nephrology, University Hospital Zurich, Switzerland

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common form of renal cystic diseases. It is associated with mutations in PKD1 and PKD2 genes that encode for the proteins polycystin-1 (PC1) and polycystin-2 (PC2). Dapagliflozin is a selective inhibitor of the sodium-glucose cotransporter 2 (SGLT2) which induces renal glycosuria.

We studied the effect of SGLT2 inhibitor Dapagliflozin on renal function and cyst progression in Han:SPRD rat model of ADPKD. Dapagliflozin (DAPA) (10 mg/kg/day) or vehicle (CON) were administered orally via gavage to 5 week old male Han:SPRD rats (n = 8/group) for a total of 5 weeks. At the end of the treatment, rats were sacrificed and kidneys were harvested for histological analysis. DAPA treated rats had a significantly higher urinary output (379 ± 8.9 vs. 25.0 ± 11.2 mI/d), glucose excretion (13.4 ± 6.2 vs. 0.3 ± 0.1 mmol/d) and water intake (72.5 ± 2.9 vs. 55.0 ± 14.7 mI/d) when compared versus controls after 5 weeks of treatment. In contrast, no changes in body weight were observed. There were no differences in urine excretions of Na+ (1.7 ± 0.5 vs. 1.2 ± 0.2 mmol/d) neither Cl- (2.4 ± 0.7 vs. 1.8 ± 0.4 mmol/d) between DAPA- and vehicle-treated rats after 5 weeks of treatment. DAPA-treated rats showed significantly higher clearances for creatinine (2.4 ± 0.3 vs. 1.1 ± 0.1 ml/min P = 0.01) and BUN (0.7 ± 0.1 vs. 0.4 ± 0.1 ml/min) after 5 weeks when compared to controls. DAPA treatment during 5 weeks showed a 2 kidney weight body weight ratio (2K/BW) increase (2.3 ± 0.3 vs. 2.0 ± 0.2 P = 0.01) compared to control. There was a reduction of cyst index (6.9%) when compared DAPA-treated with Vehicle-treated rats (20.3 ± 1.4 vs. 21.9 ± 1.2% P = 0.05).

Inhibition of glucose reabsorption with the SGLT2-specific inhibitor dapagliflozin caused significant glycosuria (Han:SPRD: SGLT2). Unexpectedly, even when the kidney weight increased, cyst index seems to decrease slightly and clearances reflect an enhanced kidney function. This suggests that there is dissociation between kidney weight and cyst growth in this model of ADPKD.

Inhibition of aerobic glycolysis with 2-deoxyglucose retards polycystic kidney disease progression in Han:SPRD rats

Meliana Riwanto, Sanika Kapoor, Daniel Rodriguez, Ilka Edenhofer, Stephan Seguerer, Rudolf P. Wüthrich

Division of Nephrology, University Hospital Zurich, Zurich, Switzerland

Autosomal dominant polycystic kidney disease (ADPKD) is a common genetic disorder characterized by the development of multiple bilateral cysts in the kidneys. This study aimed to investigate the effect of 2-deoxyglucose (2DG), a glycotoxic inhibitor, on renal function loss and cyst progression in Han:SPRD rats, a PKD model with a phenotype closely resembling human ADPKD. Male heterozygous cystic (Cy+/y) and wild-type (+/+ ) rats were administered 2DG (500 mg/kg/day) for 5 weeks (n = 10/group).

Treatment with 2DG significantly reduced kidney weights and 2/kidney total-body weight ratios and decreased renal cyst index in Cy+/y rats (27%, 21% and 48% reduction vs vehicle, respectively, p < 0.05). Cy+/y rats treated with 2DG also showed improved creatinine clearance (198 ± 0.67 vs 141 ± 0.37 p < 0.05), BUN clearance (0.69 ± 0.26 vs 0.40 ± 0.10, p < 0.01) and uric acid clearance (0.38 ± 0.20 vs 0.21 ± 0.10, p < 0.05). Interestingly, administration of 2DG led to a sustained increase in urine volume output, suggesting renal resistance to vasopressin. Immunohistochemical analysis of kidney tissues harvested from 2DG-treated Cy+/y rats showed increased phosphorylation of AMPK, a negative regulator of mTOR, and decreased ERK signaling. Moreover, in cultured primary epithelial cells from Cy+/y-rats, 2DG dose-dependently impaired cell growth (assessed by MTS assay), limited cellular proliferation (examined by BrdU assay), reduced lactate secretion and decreased ATP production. Taken together, our results show that the cystic kidneys of Han:SPRD rats display enhanced aerobic glycolysis which may play an important role in the pathogenesis of PKD. Administration of 2DG markedly delayed the loss of renal function and retarded cyst development in Han:SPRD rats with PKD. Targeting the glycolytic pathway may therefore present a novel therapeutic strategy to control cyst growth in polycystic kidney disease.
Mediator of ErbB2 Induced Cell Motility in Mineral Homeostasis
Matthias Moor1, Nancy E. Hynes2, Olivier Bonny1
1University of Lausanne, Department of Pharmacology and Toxicology, Lausanne; 2Friedrich Miescher Institut for Biomedical Research, Basel.

Background: The 33kDa mediator of ErbB2 induced cell motility (Mempo) modulates fibroblast growth factor (FGF) receptor, insulin receptor, estrogen receptor and sphinngosine1-phosphate signaling, but its physiological role is poorly understood. Inducible Mempo knock out mice showed signs of premature aging, insulin hypersensitivity and a deranged mineral metabolism similar to the phenotype of FGF-23 or klotho mutant mice, including hypercalciemia, elevated 1,25(OH) D3 and suppressed parathyroid hormone (PTH) (Haenetz B, FASEB J 2013). We tested (1) if Mempo is expressed in osteocytes that secrete FGF23 and in osteoclasts and (2) if Mempo expression can be regulated.

Methods: C57BL/6 bone marrow monocytes were isolated and differentiated to osteoclasts ex vivo by RANK ligand and colony-stimulating factor. MLO-Y4 osteocytes were grown on collagen. C57BL/6 mice were challenged with 1.69% vs 0.89% vs 0.17% dietary calcium over 7 days (group 1), with 1.5% vs 0.8% vs 0.2% dietary phosphate over 7 days (group 2), treated with 1 subcutaneous injection of 2ug/kg 1,25(OH)2-D3 (group 3) or 80 ug/kg PTH (group 4), or daily with subcutaneous injections of 15ng 17beta-Estradiol or vehicle over 5 days (group 5). Cells and tissues were prepared for qPCR and immunoblotting using specific probes and anti-Mempo antibodies respectively.

Results: Mempo was present in osteoclasts ex vivo and in osteocytes in vitro. Varying dietary calcium and phosphate load, or treating with 1,25(OH)2-D3, PTH, or estradiol treatment altered experimental control gene expression in the kidney and in the tibia, but Memo RNA and protein abundance remained unchanged.

Conclusion: Mempo contains a housekeeping gene’s function in normal mineral homeostasis but is not a responsive element to calcitropic stimuli. During the next steps, Memo will be studied in the bone of inducible whole-body Memo KO mice.

Neuropilin1 as a novel regulator of glomerular basement membrane
Monika Wnuk, Jean-Baptiste Dubuis, Valentin Djonov
Institute of Anatomy, University of Bern

Background: Neuropilin1 (Nr1p) is a transmembrane co-receptor classically implicated in the regulation of endothelial cell migration during angiogenesis and thus a potential target of anti-tumorigenic therapy. Recently, clinical trial with antiNrp1 antibodies in cancer patients had to be discontinued due to the high grade proteinuria in all patients. The aim of this study was therefore to unravel the expression pattern and role of Nrp1 in adult kidney.

Methods: AntiNrp1 neutralizing antibodies with different binding properties were applied to 2–3 weeks old mice, Control animals received mouse IgG. Kidney function was monitored following animal sacrifice after 4 weeks.

Results: In adult mouse kidney, Nrp1 was expressed in mesangial cells and pericytes of kidney peripheral capillaries in addition to already described localization in endothelium. Administration of antiNrp1 antibodies caused progressive proteinuria, however only in male mice. Kidney histology showed mild mesangial I expansion, and electron microscopy revealed thickened and folded glomerular basement membrane (GBM). The foot process and endothelial fenestrations were relatively intact. mRNA levels of lama5, agrin and nidogen were upregulated following Nrp1 blockade, whereas vegf was downregulated. Surprisingly, VEGFR2 receptor was hyperphosphorylated upon Nrp1 inhibition. Further in vitro studies with primary mesangial human and mouse cell lines showed increased cell proliferation upon Nrp1 blockade and abnormal actin reorganization and chemotaxis when Nrp1 knock down cells were stimulated with PDGFbb.

Conclusions: This study shows an unexpected role of Nrp1 in maintenance of GBM and suggests a critical involvement of mesangial Nrp1 in this process.

Oncostatin M receptor is a sensitive and early marker of kidney injury
Barbara Pedycyz1, Pang Young1, Catherine Compston1, Valerie Luyckx1, Julie Ho1, Valeria Mas1, Lin-Fu Zhu2, Donald Grynoch1, Rachel Khadaroo1, Thomas Mueller1
1University of Alberta; 2Transplantation and Nephrology, University of Manitoba, Winnipeg, Manitoba, Canada; 3University of Virginia; 4Division of Nephrology, University Hospital, Zurich

Background: Early and sensitive biomarkers for acute kidney injury are needed for diagnostic and therapeutic purposes. The IL6-family receptor Oncostatin M (OSMR) was shown to be the most significantly induced acute phase protein in kidney tissues from deceased compared to living donors.

Methods: Microarray-based gene transcription levels of OSMR in 0- hr biopsies of 67 human deceased donor kidneys were compared between groups stratified for normal, mild-to-moderate, and severely impaired function. In mice undergoing unilateral kidney clamping (AKI induced by local ischemia reperfusion) and undergoing cecal ligation and puncture (AKI induced by systemic infection) kidneys, hearts, livers and lungs were harvested at different time points post-injury and transcript levels of pre-selected injury markers were compared with OSMR expression measured by array or RT-PCR based technologies. Transcriptome changes were analyzed using GeneSpring and Ingenuity software packages.

Results: In the human 0-hr biopsies OSMR-transcript levels compared to established injury markers such as KIM1 and NGAL changed most significantly according to degree of functional impairment (corr. P <0.001). The transcriptome analysis further identified more than 60 other potential injury marker genes with similar expression patterns than OSMR (r >0.95).

The mice models also showed early expression of OSMR induced by renal ischemia or systemic infection/sepsis is associated with increased OSMR levels already at early time points (at least 3 hrs after injury) and in all investigated organs. In addition the severity of injury, as shown on histology, changes in renal function or extent of lesion induced, correlated with the degree of OSMR expression.

Conclusions: Our results indicate that OSMR is a novel, promising biomarker of organ injury, in particular reflecting degree of kidney injury at a very early time point.

Pathophysiology of Chronic Kidney Disease in MethyImalonic Aciduria (MMA)
Anke Schumann1, Alessandro Luciani1, Matthias Baumgartner1, Andrew Hall2, Olivier Devuyst1
1Institute of Physiology, University of Zurich, Zurich; Center for Integrative Human Physiology, University of Zurich, Zurich; 2Division of Metabolism and Child Health Research Center, University Children’s Hospital, Zurich; Center for Integrative Human Physiology, University of Zurich, Zurich; 3Institute of Anatomy, University of Zurich, Zurich

Background: MMA is an inborn error of metabolism caused by mutations in the mitochondrial enzyme Methylmalonyl-CoA Mutase (MCM) or by mutations affecting the synthesis of its cofactor adenosylcobalamin. MMA leads to life-threatening metabolic crisis occurring in the neonatal period, with chronic kidney disease (CKD) and end stage renal failure as classical long-term complications. The role of MCM in the kidney and the pathophysiology of CKD associated with MMA is unknown.

Methods: We characterized the expression profile of MCM in mouse kidney and its subcellular distribution in the human proximal tubule cell line HK2 using RT-qPCR, immunoblot analysis and STEM microscopy. We next used renal cells obtained from the urine of MMA patients as a disease model to characterize the pathophysiology of MMA.

Results: MCM was detected in the proximal tubule and in distal nephron segments of the mouse kidney identified by co-distribution of specific markers. Co-staining with TOM20, an outer membrane mitochondrial import receptor, evidenced that MCM is localized in the mitochondrial matrix. Enzymatic MCM activity measurements in renal cells showed increased cell proliferation upon Nrp1 blockade and abnormal actin reorganization and chemotaxis when Nrp1 knock down cells were stimulated with PDGFbb.

Conclusion: These studies reveal a complex distribution of MCM in the mitochondria of epithelial cells lining various renal tubular segments. Urinary cells derived from MMA patients show defective handling of starvation, with increased oxidative stress and defective mitochondria. These data provide novel insights into the mechanisms of CKD in MMA.
Proteomic Signature of Hypertension-induced Damage in the Two-Kidney, One-Clip (2K1C) Rat Model
Heidrun Vethe1, Kenneth Finne1, Trude Skogstrand2, Marc Vaude3, Bjørn Egil Vike3, Michael Hultström1, Sandrine Placier1, Andreas Scherer2, Olav Tenstad1, Hans-Peter Marti1
1Department of Clinical Medicine, University of Bergen, Bergen, Norway; 2Department of Biomedicine, University of Bergen, Bergen, Norway; 3Department of Medical Cell Biology, Uppsala University, and Anaesthesiology and Intensive Care Medicine, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden; 4INSERM U702, Hopital Tenon, Paris, France; 5Spheronics, Kombolait, Finland

Background: Hypertensive nephrosclerosis is one of the most frequent causes of chronic kidney failure leading to end-stage renal disease (ESRD). Proteome analysis potentially improves the pathophysiological understanding and diagnostic precision of this disorder. In the present exploratory study we investigated experimental nephrosclerosis in the Two-Kidney, One-Clip (2K1C) hypertensive rat model.

Methods: The renal cortex proteome from juxtamedullary cortex (JMC) and outer cortex (OC) of 2K1C male Wistar-Hannover rats (n = 4) was compared with sham-operated controls (n = 6), using mass spectrometry-based quantitative proteomics. We combined a high abundant plasma protein depletion strategy with an extended liquid chromatographic gradient to improve peptide and protein identification. Immunohistology was used for independent confirmation of abundance.

Results: We identified 1,724 proteins, of which 1,434 were quantified with ≥2 unique peptides. Comparative proteomics revealed 608 proteins, including the PDGFR-β signalling pathway, with different abundances between the non-clipped kidney of hypertensive 2K1C rats and the corresponding kidney of normotensive controls (p <0.05, absolute fold change ≥1.5). Among the most significantly altered proteins in whole cortex were peristin, transgelin, and creatine kinase B-type. Relative abundance of peristin alone allowed clear classification of 2K1C and controls. Enrichment of peristin in 2K1C rats was verified by immunohistology showing positivity especially around fibrotic vessels.

Conclusion: The proteome is altered in hypertension-induced kidney damage. We propose peristin, especially in combination with transgelin and creatine kinase B-type as possible proteomic classifier to distinguish hypertensive nephrosclerosis from normal tissue. This classifier needs to be further validated with respect to early diagnosis of fibrosis, prognosis, and its potential as a novel molecular target for pharmacological interventions.

Sex-specific expression of genes involved in uric acid handling in mice
Muriel Auberson, Candice Stoudmann, Olivier Bonny
University of Lausanne, Department of Pharmacology and Toxicology, Rue du Bugnon 27

Background: In several species, females have lower serum uric acid (SUA) levels compared to males, an observation largely dependent on sex hormones, but independent of the presence of uricase. In human, this is illustrated by the fact that men are more prone to develop gout flares or uric acid kidney stones. The underlying mechanism is however not precisely known and we ask here whether production, degradation or excretion of uric acid may account for the observed difference between genders.

Methods: We used C57BL/6N mice to address the role of the liver, ileum, colon and the kidney in sex-specific difference in SUA levels.

Results: We first confirmed that SUA concentrations are 36.1 ± 18.7% lower in female than male mice. Interestingly, the fractional excretion of uric acid was identical between males and females, suggesting that the overall renal tubular function was similar. We then performed a detailed expression analysis of genes involved in uric acid production (XDH), degradation (UOX) or transport in the liver, ileum, colon and the kidney (MRP4, ABCG2, GLUT9a, GLUT9b, URAT1, OAT1, OAT3, OAT10, NPT1, NPT4). Several genes were found to display a sex-dependent expression pattern eventually suggesting that females may have increased MRP4-mediated UA excretion in the intestine.

Conclusions: Our results may have consequences beyond uric acid handling as several of these transporters are also involved in drug secretion. Sex-differences in the expression of these transporters should be taken into consideration.

Renal sensitivity to orthostatic stress: a comparison of neuro-hormonal and renal hemodynamic responses between obese patients and healthy volunteers
Nima Vakilzadeh1, Yann Vuignier1, Marc Maillard2, Eric Grouzmann3, Vittorio Giusti4, Michel Burnier5
1Service of Nephrology and Hypertension, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; 2Internal Medicine Department, Valais Hospital, Switzerland; 3Clinical Pharmacology, Lausanne University Hospital, Switzerland; 4Care and rehabilitation center, Intercantonal Hospital of Broye, Switzerland

Objective: Obesity is associated with an increased risk of developing hypertension and chronic kidney disease. However the mechanisms involved in the pathogenesis of obesity-related hypertension are fully elucidated. Animal studies have suggested that the sympathetic nervous system and the ability to excrete sodium are key factors elucidated. Animal studies have suggested that the sympathetic nervous system and the ability to excrete sodium are key factors involved in the development of hypertension.

The objective of the study was to compare neuro-hormonal and renal responses to orthostatic stress induced by lower body negative pressure (LBNP) in healthy volunteers and obese patients.

Method and design: This was a single center prospective study. Healthy volunteers and obese patients were included in a 1:1 ratio. Participants’ characteristics, lepton and adiponectin were measured at baseline. Blood pressure (BP), heart rate, plasma renin activity (PRA), plasma aldosterone, norepinephrine (NE), sodium excretion, glomerular filtration rate (GFR), insulin clearance and renal plasma flow (RPF, PAG clearance) were measured at baseline and after one hour of LBNP.

Results: 48 patients were included in this study, 25 healthy controls (HC) and 23 obese patients (OB). Mean BMI was 22.0 ± 2.2 kg/m² in HC and 34.7 ± 4.6 kg/m² in OB (p <0.05). Hemodynamic, neuro-hormonal and renal responses to LBNP are shown in table 1.

Table 1: hemodynamic, renal and neuro-hormonal responses to LBNP in HC and OB

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>LBNP</th>
<th>Baseline</th>
<th>OB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td>110±9</td>
<td>113±10*</td>
<td>128±15*</td>
<td>134±19*</td>
</tr>
<tr>
<td><strong>Diastolic BP (mmHg)</strong></td>
<td>64±8</td>
<td>69±7*</td>
<td>77±11*</td>
<td>84±13*</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>63±8</td>
<td>61±8</td>
<td>65±7</td>
<td>68±9*</td>
</tr>
<tr>
<td><strong>Glomerular filtration rate (ml/min)</strong></td>
<td>102±21</td>
<td>90±29*</td>
<td>102±24</td>
<td>102±37</td>
</tr>
<tr>
<td><strong>Renal plasma flow (ml/min)</strong></td>
<td>576 (434-675)</td>
<td>514 (349-605)*</td>
<td>611 (284-715)</td>
<td>562 (415-656)</td>
</tr>
<tr>
<td><strong>Sodium excretion (µmol/min)</strong></td>
<td>23±7</td>
<td>21±192*</td>
<td>234±113</td>
<td>214±149</td>
</tr>
<tr>
<td><strong>NE (nM)</strong></td>
<td>1.14 (0.9-1.37)</td>
<td>1.46 (1.17-2.1)*</td>
<td>1.03 (0.76-1.46)</td>
<td>1.54 (1.07-1.82)*</td>
</tr>
<tr>
<td><strong>PRA (ng/ml/min)</strong></td>
<td>0.35 (0.3-0.5)</td>
<td>0.5 (0.25-0.8)*</td>
<td>0.5 (0.08-0.6)</td>
<td>0.5 (0.2-1.0)*</td>
</tr>
<tr>
<td><strong>Aldosterone (ng/ml)</strong></td>
<td>28.5 (21.0-50.9)</td>
<td>29.5 (20.8-56.1)</td>
<td>39.8 (18.0-57.2)</td>
<td>42.4 (27.3-51.8)</td>
</tr>
</tbody>
</table>

Data are means ± SD or medians and interquartile range. HC: healthy control, OB: obese, LBNP: lower Body Negative Pressure, BP: blood pressure, NE: norepinephrine, PRA: plasma renin activity. * P<0.05 vs baseline, † P<0.05 vs HC
At baseline, systolic BP, diastolic BP were significantly higher in OBT than in HC. During LBNP, systolic and diastolic BP increased in both groups. Heart rate increased in OBT but not in HC (+2.9 vs. −1.2 beats/min, p = 0.01). GFR and RPF decreased significantly in HC, respectively (−12 ± 26 ml/min); −85 ml/min (−152±3), but not in OBT patients.

Conclusion: Obese patients seem to be able to maintain GFR and sodium excretion compared to healthy volunteer during an orthostatic stress. This may be secondary to increased systemic blood pressure and/or cardiac output as suggested by increase in heart rate during the LBNP period.

Distinct radiological CT-patterns of Pneumocystis jirovecii pneumonia between Renal transplant recipients and HIV-positive patients

Sypnoid Arampatzis1, Lukas Ebner1, Andrä Rauch1, Hansjakob Ferrer1, Stefan Weiler1, Johannes Heverhagen1, Uyen Huynh-D01, Andreas Christe1
1Department of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Bern University Hospital, Switzerland; 2Department of Diagnostic, Interventional and Pediatric Radiology, Inselspital, Bern University Hospital, Switzerland; 3University Clinic for transplant immunology and nephrology, Clinic for transplant immunology and nephrology, University Hospital of Basel-Liestal, Switzerland
Background: Pneumocystis jirovecii pneumonia (PCP) is a fungal infection with potentially life-threatening complications. Renal transplant recipients (RTR) and individuals who are immunocompromised (i.e. HIV patients) are at substantial risk for PCP. Limited data exist on the comparison of radiological pattern based on the distinct immunological etiologies in well-characterized groups, such as RTR and HIV patients.
Aim: To compare CT patterns of PCP between HIV-positive patients and renal transplant recipients (RTR).
Methods: Retrospective analysis of 40 immunocompromised patients (16HIV, 24RTR) presenting with CT-radiographic findings and established PCP diagnosis during hospitalization. Patient data were obtained from the Bernese HIV- and RTR-cohort of the University Hospital of Bern. Classification of the lung patterns was performed according to the Fleischner society recommendations.
Results: In 40 immunocompromised patients we identified a distinct distribution in the lungs of the HIV patients infected with PCP, which showed significantly more areas with a diffuse pattern of scattering (81 ± 10% HIV vs. 25 ± 9% RTR; p = 0.02). Multifocal pattern distribution, central lung parenchyma affection, lung peripheral involvement, cysts and subpleural spearing did not differ significantly between the groups. Ground glass nodules >5 mm were significantly more common in the HIV patients than the RTR (69 ± 12% vs. 4 ± 4%; p = 0.0004). Enlarged hilar lymph nodes were a distinct characteristic of HIV-associated PCP, since no such finding was identified in RTR (0% vs. 44 ± 12%; p = 0.0123).
Conclusions: Radiographic differences in PCP are present between HIV-patients and RTR. Distinct patterns should be considered in the differential diagnosis of pulmonary infiltrates. These differences potentially reflect immunological differences in the host immune response.
and progression rate were increased 2-fold for TCC naïve (TCCn) and for patients with pretransplant history of TCC (hTCC) 3-fold and 2-fold, respectively. TCC related death occurred in 52% of TCCn and in 16.7% of hTCC patients. Hematuria was the main symptom leading to detection of TCC. The major risk factors were smoking and analgetic abuse. TCC associated graft failure was seen in 13% of patients.

Conclusions: TCC in renal transplant patients is associated with an increased recurrence as well progression risk and with a high tumor related mortality. TCC in these patients therefore requires prudent treatment and a rigid surveillance. Dip stick analysis for hematuria as well as urine cytology should be incorporated in the regular follow-up exams.

Outcomes at 3-years in EBV+ Recipients of Deceased Donor Kidneys from Two Randomized Trials (BENEFIT and BENEFIT EXT) Comparing Belatacept vs Cyclosporine

Background: Belatacept (bela; less intensive [LI] regimen) is approved to treat EBV+ adult kidney transplant patients (pts). Here we present post-hoc analyses of 3-year outcomes in EBV+ pts in the pooled populations of BENEFIT and BENEFIT-EXT who received a deceased donor kidney.

Methods: In BENEFIT, pts received living donor (n = 385) or SCD kidneys (n = 281). BENEFIT-EXT (N = 543), pts received ECD kidneys (defined as UNOS criteria ECD, cold ischemia time ≥24 hour, or donation after cardiac death). In both trials, pts were randomized to more intensive (MI) or LI bela or CsA. Here we evaluated the pooled cohort for pt and graft survival, cGFR, acute rejection (AR), and a composite end point (EP): death, graft loss or GFR <30.

Results: In this cohort, 250 MI, 247 LI, and 249 CsA pts were EBV+ at the time of transplant and received a deceased donor kidney. Pt/graft survival at Month (M) 36: 211 (84%) MI, 217 (88%) LI, and 205 (82%) CsA. The rate of AR through M36 was 22% MI, 17% LI, 14% CsA. Mean (SD) MDRD cGFR at M36 was 50.5 (30) MI, 51.6 (27) LI, 35.0 (23) mL/min/1.73 m² CsA. Fewer bela-treated pts vs CsA reached the composite EP (figure). Rates of serious adverse events were generally similar across treatment arms.

Conclusions: Results of this post-hoc analysis demonstrate the following for EBV+ pts in BENEFIT and BENEFIT-EXT receiving a deceased donor kidney, vs CsA: similar pt/graft survival, improved renal function for both bela regimens, and similar rate of AR for both bela regimens (approved LI regimen only). For both bela regimens, the rate of composite EP was lower with bela vs CsA. The positive outcomes in this subset of EBV+ pts are consistent with results observed with bela in the overall populations of BENEFIT and BENEFIT-EXT.
Outcomes at 3-years in EBV+ Recipients of UNOS Criteria ECD Kidneys from a Randomized Trial (BENEFIT-EXT) Comparing Belatacept vs Cyclosporine
Ferdinand Mühbacher,1 Antoine Durnbach,2 Sander Florman,3 José Medina Pestana,3 Martin Polinsky,4 Bernard Charpentier1 1Medical University of Vienna, Austria; 2University Hospital of Bicètre, France; 3Mount Sinai Medical Center, USA; 4Hospital do Rim e Hipertensão, Brazil; 5Bristol-Myers Squibb, USA
Background: Belatacept (bela; less intensive [LI] regimen) is approved to treat EBV+ adult kidney transplant patients (pts). Here we present post-hoc analyses of 3-year outcomes for EBV+ pts in BENEFIT-EXT who received deceased donor kidneys consistent with UNOS ECD criteria.
Methods: In BENEFIT-EXT, 543 pts received ECD kidneys per UNOS criteria, anticipated cold ischemia time (CIT) >24 hrs, or donation after cardiac death. UNOS criteria included age ≥60 years or age 50–59 with ≥2 other risk factors (cerebrovascular accident, hypertension, or diabetes). Pt and graft survival, renal function, and serious adverse events were generally similar across treatment arms.
Results: Of 454 evaluable pts, 54 (12%) were EBV+ and CMV−. Rates of EBV reactivation were similar across treatment arms. In the bela MI regimen, 50% of pts were EBV+ compared with 29% in the LI regimen (p = 0.003). Incidence of EBV-related disease was twofold higher in the bela MI compared with bela LI (3.9% vs 1.7%, p = 0.047). Occurrence of urinary tract infections (60% vs 32% of patients, p = 0.047) and AR, were followed at defined visits in the first year post-transplant.
Results: Patients (n = 90; mean age 48 ± 13 years; 63% males) had a baseline eGFR of 52.7 ± 15.0 mL/min/1.73 m². By DXA (lumbar spine) 37% were osteopenic and 11% osteoporotic. Baseline calcium (2.32 ± 0.19 mmol/l), phosphate (0.58 ± 0.51 µg/l) and PTH (153.7 ± 145.2 ng/l) indicated persistent hyperparathyroidism. Denosumab-treated patients had significantly lower plasma levels of the bone resorption marker β-CTX (0.22 ± 0.20 vs 0.79 ± 0.51 µg/l; p <0.001) and the bone formation markers P1NP and BSAP (9.3 ± 6.9 vs 20.5 ± 11.5 µg/l; p <0.001) at 12 months. Denosumab treatment was well tolerated, except for a higher occurrence of urinary tract infections (60% vs 32% of patients, p = 0.047).
Conclusions: The POSTOP trial represents the first study to investigate whether denosumab prevents BMD loss in the first year after kidney transplantation. Measurements of β-CTX, P1NP and BSAP can be used to monitor the effect of denosumab treatment. Further analyses are needed to correlate the change of these biomarkers with the effect of denosumab on BMD.
Risk stratification for rejection and infection after kidney transplantation

Pietro Cippitì1, Marc Schiesier2, Teun Van Gelder1, Nicolas Müller3, Claude Caot4, Corrado Bernasconi5, Thomas Fehr1
1University Hospital Zurich, Division of Nephrology; 2University Hospital Zurich, Division of Visceral & Transplantation Surgery; 3University Hospital Malmö, Sweden; 4University Hospital Zurich, Division of Infectious Diseases; 5Praxis Riesbach, Zurich; 6Limes Medical Research, Zurich

Background: Current immunosuppressive therapy is very effective in preventing acute renal allograft rejection, but it is inevitably related to adverse effects. Keeping the delicate balance between the control of rejection and the risk for infections emerged as a critical aim in modern transplantation medicine. The aim of this study was to establish a risk stratification model for rejection and infection after kidney transplantation.

Methods: In a post-hoc analysis of the ELITE-Symphony trial (n = 1190) we characterized the incidence and pre-transplant predictors of severe infection and acute rejection episodes in the first year after transplantation with the goal of identifying patient groups that may benefit from tailored immunosuppression protocols. The approach was validated using internal data as well as an external study population from the GFDC trial (n = 901).

Results: In the first year after kidney transplantation infections were frequent (incidence 25.5%) and the principal cause of death in kidney transplant recipients (43.2% of all deaths). Recipient age, donor type, HLA-mismatches and type of immunosuppressive therapy were identified as independent pre-transplant risk factors. The validation cohort was found to be a good representation for the applicability of the proposed risk model to an independent cohort.

Conclusions: An integrated assessment of the risk for rejection and infection is necessary to improve clinical management of transplant recipients and to design future transplant studies. The proposed risk stratification approach might help personalize immunosuppressive therapy.

Role of lymphotixin in renal allograft rejection

Harald Seeger1, Gitta Seleznek2, Maja Lindenmeyer3, Clemens Cohen4, Carsten Jäckel5, Peter Nelson6, Jin Chen7, Ilka Edenhofe8, Nicolas Kozakovski9, Heinz Regele10, Georg Böhming11, Judith Bauer12, Rudolf P. Wüthrich13, Thomas Fehr14, Matthias Heikenwälder15, Stephan Segerer1
1Division of Nephrology, University Hospital, Zurich; 2Division of Visceral & Transplantation Surgery, Swiss Hepato-Pancreato-Biliary Center, Zurich, Switzerland; 3Institute of Pathology, University of Zurich, Switzerland; 4Klinikum Harlaching, Sanatoriumspaz 2, 81545 München; 5Klinikum der Universität Muenchen, Medizinische Klinik und Poliklinik IV; 6Institute of Physiology, University of Zurich, Switzerland; 7Clinical Institute of Pathology, University of Vienna, Vienna, Austria; 8Division of Nephrology and Dialysis, Department of Medicine III, Medical University Vienna, Austria; 9Institute of Virology, TUM, Helmholtzentrum, Munich, Germany; 10Department Innere Medizin, Kantonsspital Graubünden, Chur

Background: Kidney transplantation is the most common form of solid organ transplantation and the majority of kidney transplant recipients are treated with calcineurin inhibitors in the initial phase of T-cell mediated rejection of chronic allograft injury in kidney transplant recipients. The present study was aimed to evaluate the frequency of chronic allograft dysfunction and to clarify the pathophysiological mechanisms involved.

Methods and Results: We investigated differentially expressed components of the LT system in CDNA microarrays from human renal allograft biopsies. We were able to demonstrate the upregulation of LTbeta, LIGHT, HVEM and TNF receptors and HLA class Il and Il2 receptors in acute and chronic rejection in human renal biopsies. In addition we found evidence for the activation of the NFκappB pathway, most likely a consequence of LTbeta receptor activation. By RT-PCR robust upregulation of IL-6, IL-10, IL-1β and IL-6 was characterized by strong production of LTalpha, TNF, LIGHT, HVEM, BTLA, CXCL13, CCR7 and CCL21, whereas the second pattern was characterized by expression of LTbeta and its receptor, TNF receptors 1 and 2, MADCAM and TROY. Finally, activation of the T-cell receptor signaling was modeled of renal transplantation indicating a species independent mechanism.

Conclusion: LTβ and downstream target genes are upregulated in acute and chronic allograft injury in human and in mouse renal allografts. Whether LTβ promote or ameliorate allograft rejection in unknown. The mouse renal allograft model will help to define the functional role of LTs in future studies.
The inflammatory burden determined by urinary CXCL10 chemokine levels predicts long-term renal allograft outcome

Patricia Hirt-Minkowski1, Julie Ho2, Ang Gao3, Patrizia Amico3, Michael T. Koller4, Helmut Hopfer4, David Rush5, Peter Nickerson5, Stefan Schaub5
1Clinic for Transplant Immunology and Nephrology, University Hospital of Basel, Switzerland; 2Transplantation and Nephrology, University of Manitoba, Winnipeg, Manitoba, Canada; 3Manitoba Centre for Proteomics and Systems Biology, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada; 4Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland; 5Institute for Pathology, University Hospital Basel, Basel, Switzerland

Background: Even nowadays, graft loss is a clinically evident problem. We have previously demonstrated that the urinary CXCL10 chemokine is a biomarker for clinical and subclinical tubulo-interstitial inflammation. The aim of the current study was to investigate whether urinary CXCL10 levels measured within the first 6 months – reflecting the early inflammatory burden – can predict long-term outcome.

Methods: The study cohort consisted of 154 kidney allograft recipients with two surveillance biopsies/corresponding urine specimens until six months post-transplant (i.e. performed at three and six months). Outcomes were prospectively determined during a minimal follow-up of five years (range 5–8.5 y). The sum of urinary CXCL10 concentrations obtained at biopsy time-points was calculated and the arithmetic mean used for determining the “inflammatory burden.” Evaluated endpoints were graft loss; decline of renal function (i.e. >20% decrease of eGFR between six months and last follow-up); clinically evident late rejection (i.e. after six months post-transplant).

Results: After a minimal follow-up of five years 43/154 patients reached the combined graft endpoint (28%). CXCL10 levels were significantly higher in these patients compared to kidney allograft recipients with a stable post-transplant course (median urinary CXCL10/creatinine ratio of 2.0 ng/mmol vs. 0.9 ng/mmol; p = 0.005).

In a multivariable cox-regression model including baseline and histological variables independent predictors of combined graft endpoint were high CXCL10 levels (HR of 1.14 (95% CI, 1.06–1.21; p = 0.001)) and total HLA-mismatches (HR of 1.36 (95% CI, 1.04–1.79; p = 0.03)), while donor age/weight, presence of BKV viremia, proteinuria at six months and occurrence of early acute rejection were not (p >0.05).

Conclusion: The early inflammatory burden determined by urinary CXCL10 levels is an independent and strong predictor of long-term renal allograft outcome.

What should the post-transplant creatinine be?
An approach to better assess kidney transplant function
Scott-Oliver Grebe1, Riyad Ylsehli2, Valerie Luyckx3, Zija Jacal4, Thomas Mueller1
1Helios-Clinics, University of Witten-Herdecke, Germany; 2King Saud University, Riyadh, Saudi Arabia; 3University of Alberta, Edmonton, Canada; 4Athabasca University, Athabasca, Canada; 5Division of Nephrology, University Hospital, Zurich

Background: Knowledge of an optimal expected serum creatinine (SCr) would be useful to detect early renal dysfunction after transplantation. Current measurements of post-transplant function rely exclusively on the recipient’s SCr and derived calculations (eGFR), based on recipient age, weight and gender. Renal function post-transplant, however, also depends on the donor supply of functioning nephrons and adaptation in GFR of a single kidney.

Methods: We developed a formula to predict the optimal expected SCr post-transplant derived from donor and recipient Cockcroft-Gault GFRs, and adjusted for the single kidney adaptive response, obtained from measurements in 27 living donors pre- and post-donation. We compared the expected SCr with the lowest observed SCr in a cohort of living (79) and deceased (67) donor allograft recipients followed over five years.

Results: The remaining, native kidneys showed a highly reproducible adaptive response of about 36% increase in GFR post-donation in the living donors. At time of transplantation donor and recipient demographics were similar between the living and deceased donor groups. Expected SCr correlated well with the observed SCr in both living and deceased donor kidney recipients, however correlation was stronger among living donor kidney recipients. Recipient to donor body weight ratio was significantly associated with the difference between expected and observed SCr, suggesting that recipient body weight is a major predictor of post-transplant renal function. The difference between expected and observed SCr was significantly greater among deceased donor kidney recipients, suggesting poorer function in these patients, which was not detected by SCr or estimated GFR (CKD-EPI, MDRD or GG formulas alone).

Conclusions: Calculation of expected renal function for a given donor-recipient combination adds relevant information to assessment of allograft function. Future studies will permit determination of a threshold difference between expected and observed SCr that should trigger investigation and potential intervention to improve allograft function.
NierensteinZentrum
Zürich
PD Dr. Bernhard Hess

HIRSLANDEN
KLINIK IM PARK

Questionnaire sent to recurrent calcium stone formers

1. To what extent (%) did you really understand the given information regarding the development of your kidney stone disease?
   - over 80% ☐
   - 60–80% ☐
   - 40–60% ☐
   - 20–40% ☐
   - <20% ☐

2. To what extent (%) did you adhere to the given recommendations with respect to changes in eating/drinking habits and lifestyle (stress)?
   - over 80% ☐
   - 60–80% ☐
   - 40–60% ☐
   - 20–40% ☐
   - <20% ☐

3. How many days per week did you follow recommendations to 100%?
   - 5–7 days ☐
   - 4–5 days ☐
   - 3–4 days ☐
   - 1–2 days ☐
   - less than 1 day ☐

4. What did you indeed change regarding eating/drinking habits and lifestyle?
   - Higher fluid intake
   - More calcium (milk and milk products)
   - Less oxalate
   - Less meat protein (very rich)
   - More vegetables and salad
   - More fruits
   - Reduced psychosocial stress

5. How many days per week did you take medication, if prescribed?
   - 5–7 days ☐
   - 4–5 days ☐
   - 3–4 days ☐
   - 1–2 days ☐
   - less than 1 day ☐

6. Would you recommend such a consultation to other stone formers?
   - YES ☐
   - Rather yes ☐
   - Rather no ☐
   - NO ☐

FGF23 and markers of phosphate and calcium homeostasis in subjects with preserved renal function

1Department of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Bern University Hospital and University of Bern, Switzerland; 2Service of Nephrology, University Hospital of Lausanne (CHUV), Switzerland; 3Service of Nephrology, University Hospital of Geneva (HUG), Switzerland; 4Institute of Social and Preventive Medicine (IUMSP), University of Lausanne, Switzerland; 5Cardiology, Department of Specialties of Internal Medicine, Geneva University Hospital (HUG), Switzerland; 6Service of Nephrology, University Hospital of Geneva (HUG), Switzerland

Background: FGF23 is a bone-derived hormone that causes phosphaturia, inhibition of 1,25-OH Vitamin D synthesis, reduction of PTH secretion and induction of left ventricular hypertrophy. The study of FGF23 regulation in adults with preserved renal function has received little attention thus far.

Methods: We examined cross-sectionally in 1128 participants of the SKIPOGH cohort, a large family-based multicenter observational study, the associations of c-terminal FGF23 levels with markers of diet, mineral metabolism and renal function. For statistical analysis we constructed mixed linear models with log transformed FGF23 as the dependent variable and family as random effect.

Results: Mean eGFR (CKD-EPI) was 96.3 ml/min/1.73 m² (SD 17.8 ml/min/1.73 m²), mean FGF23 levels were 98.1 RU/ml (SD 97.3 RU/ml). Log FGF23 levels were associated inversely with eGFR (β: –0.01, SE: 0.001; p = 5.62x10-11). In multivariate analysis adjusting for age, gender, BMI and eGFR, higher FGF23 levels were positively associated with plasma phosphate levels (β: 0.35, SE: 0.09; p = 6.99x10-4) but not with phosphate intake, 24h phosphate excretion or fractional excretion of phosphate. Interestingly, FGF23 was also independently associated with plasma calcium (β: 0.36, SE: 0.16; p = 0.002), 24h calcium excretion (β: –0.02, SE: 0.01; p = 9.07x10-4) and fractional excretion of calcium (β: –0.05, SE: 0.01; p = 1.62x10-4) but not with 25-OH Vitamin D.

Conclusions: We identified a novel association of FGF23 with plasma calcium and calcium excretion in participants with largely preserved renal function. While FGF23 levels were positively associated with plasma phosphate levels, we surprisingly found no association of FGF23 with fractional excretion of phosphorus. Thus, in subjects with preserved renal function, FGF23 may affect plasma phosphate levels independently of renal phosphate excretion. Measurements of PTH and 1,25-OH Vitamin D in this cohort will hopefully shed more light on this interesting novel aspects of FGF23 physiology.
Cytochrome P450 3A4/5 (CYP3A4/5) activity is associated with white coat blood pressure in a Swiss population-based study (SKIPOGH Study)

Yassine Bouaouit 1, Belen Ponte 1, Daniel Ackermann 1, Menno Pruijm 2, Idiris Guesous 3, Georg Ehret 4, Fred Paccaud 2, Antoine Peuchere-Bertschi 1, Bruno Vogt 5, Michel Burnier 5, Markus Mohaupt 5, Pierre-Yves Martin 6, Murielle Bochud 7

1 Division of Nephrology, Geneva University Hospitals, Geneva, Switzerland; 2 Department of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, University of Bern, Bern, Switzerland; 3 Department of Clinical Research, University of Bern, Bern, Switzerland; 4 Service of Nephrology and Hypertension, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; 5 Unit of Population Epidemiology, Department of Community Medicine and Primary Care and Emergency Medicine, University Hospital of Geneva, Geneva, Switzerland; 6 Cardiology, Department of Specialties of Internal Medicine, Geneva University Hospitals, Geneva, Switzerland; 7 Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, MD, USA; 8 Institute of Social and Preventive Medicine (IUMSP), University of Lausanne, Switzerland; 9 Hypertension Unit, Geneva University Hospitals, Geneva, Switzerland

Background: Animal studies suggest that CYP3A4/3A5 activity could play a role in arterial hypertension. 68-hydroxycortisol/cortisol ratio is a known marker of CYP3A4/3A5 activity, which can be induced by the pregnane X nuclear receptor (PXR). We investigated the association of various kidney function parameters with CYP3A4/3A5 activity in a Swiss population-based sample.

Methods: SKIPOGH (Swiss Kidney Project on Genes in Hypertension) is a family-based multi-centric cross-sectional study. Office and daytime ambulatory blood pressure (BP) were measured by validated devices. We used the urinary 68-hydroxycortisol/cortisol ratio to estimate CYP3A4/3A5 activity. We analyzed the association of office and ambulatory daytime systolic BP (SBP), diastolic BP (DBP), heart rate (HR), proportional white-coat effect (office BP-mean ambulatory SBP/mean ambulatory DBP) with transformed CYP3A4/3A5 activity using mixed linear regression to account for familial correlations. Analyses were adjusted for age, sex, body mass index (BMI), study centre, renal function, comedication and smoking status.

Results: The 254 men and 288 women included in this analysis had mean (±SD) age of 48.0 ± 18.2 and 49.7 ± 17.3 years and mean BMI of 26.0 (3.8) and 24.3 (4.4) kg/m², respectively. Mean SBP/DBP was 119.3 (17.2)/75.2 (9.3) mm Hg for office, 120.8 (12.7)/79.2 (8.4) for daytime and 132.1 (12.1)/84.7 (10.1) for the white-coat effects. Office, but not daytime ambulatory, SBP/DBP were associated negatively with log-day CYP3A4/3A5 activity (P < 0.05). White-coat effects were associated negatively with log-day CYP3A4/3A5 activity (P < 0.001).

Conclusions: We found office SBP/DBP and white-coat effects to be associated negatively with estimated day CYP3A4/3A5 activity. These results may reflect regulation of CYP3A4/3A5 activity through cross-talks between glucocorticoid receptor (GR) and PXR. Our findings are in line with a potential involvement of cytochrome P450 enzymes in blood pressure regulation, in particular when stress-induced.

Taste acceptability of pulverized brand-name and generic drugs containing amlopidine or candesartan

Sebastian A.G. Lava 1, Peter Uuestuen 2, Alessandra Ferrarin 2, Maristella Santì 3, Chiara Mardegan 4, Mario G. Bianchetti 2, Giacomo D. Simonetti 2

1 Pediatric Nephrology, University Children’s Hospital Bern and University of Bern, Switzerland; 2 Pediatric Department of Southern Switzerland, Bellinzona, Switzerland

Background: Trials with pulverized brand-name antihypertensive drugs among children suggest that, from the perspective of taste acceptability, crushed candesartan, chlortalidone, or hydrochlorothiazide were immunologically stained for Ang (monoclonal antibody) and contained for tyrosine hydroxylase (TH) or synaptophysin (SYN) to identify a catecholaminergic phenotype using fluorescent light or laser scanning microscopy. Ang-I-V concentrations were determined by tissue extraction, HPLC and radioimmunoassay.

Methods: Human right atrium specimens (n = 7, cardiac surgery) were immunohistochemically stained for Ang (monoclonal antibody) and contained for tyrosine hydroxylase (TH) or synaptophysin (SYN) to identify a catecholaminergic phenotype using fluorescent light or laser scanning microscopy. Ang-I-V concentrations were determined by tissue extraction, HPLC and radioimmunoassay.

Results: Atrial autonomic fibers and ganglionic cells stained either positive for TH or Ang or both. SYN and TH stainings suggested colocalization in catecholaminergic fibers. Ang-positive fibers were thicker than exclusively catecholaminergic fibers and, if varicose, showed fewer and larger varicosities. Epicardial Ang-positive fibers were grouped within bundles, mostly non-varicose and TH-positive. In the myocardiurn, Ang-positive fibers were infrequent, mainly non- varicose and TH-negative. These fibers were accompanied by numerous highly varicose, purely catecholaminergic fibers suggesting local neurotransmitter interaction. The perivascular plexus contained Ang-positive, mostly non-varicose, and numerous exclusively TH-positive and Ang-positive fibers co-localized Ang and TH. Subendocardial Ang-positive fibers were mainly non-varicose and TH-negative except for clusters of (1) highly varicose tortuous or spouting fibers, or (2) groupings of thin, palisade-forming fibers that resembledafferent terminals. Tissue Ang I and Ang II concentrations were 6.2 ± 2.6 and 156.4 ± 174.1, Ang III-V concentrations <2.9 fmo/l.

Conclusions: Angiotensin fibers innervate the human right atrium and are catecholaminergic or non-catecholaminergic (probably afferent or parasympathetic). Intracardiac neuronal Ang II-release may contribute to atrial Ang concentrations and may reset atrial autonomic baroreceptor reflexes via synaptic Ang receptors to control blood pressure.

Angiotensinergic innervation of the human right atrium, atrial angiotensins and implications for baroreceptor control of blood pressure

Jürgen Bohlander 1, Jürg Nussberger 2, Hendrik Teværea 3, Hans Imboden 4

1 Institute of Cell Biology, University of Bern, Bern, Switzerland; 2 Department of Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; 3 Department of Cardiovascular Surgery, Inselspital, University of Bern, Bern, Switzerland

Background: The autonomic innervation of the heart controls cardiac function and arterial blood pressure by autonomic baroreflexes originating in the right atrium and central vessels. Angiotensin II (Ang) is a neuropeptide co-transmitter of sympathetic fibers and may modulate intracardiac neurotransmission via its synaptic Ang receptors. The presence of angiotensinergic fibers in the human atria and their phenotype and potential function are not known.

Methods: Human right atrium specimens (n = 7, cardiac surgery) were immunohistochemically stained for Ang (monoclonal antibody) and contained for tyrosine hydroxylase (TH) or synaptophysin (SYN) to identify a catecholaminergic phenotype using fluorescent light or laser scanning microscopy. Ang-I-V concentrations were determined by tissue extraction, HPLC and radioimmunoassay.

Results: Atrial autonomic fibers and ganglionic cells stained either positive for TH or Ang or both. SYN and TH stainings suggested colocalization in catecholaminergic fibers. Ang-positive fibers were thicker than exclusively catecholaminergic fibers and, if varicose, showed fewer and larger varicosities. Epicardial Ang-positive fibers were grouped within bundles, mostly non-varicose and TH-positive. In the myocardiurn, Ang-positive fibers were infrequent, mainly non- varicose and TH-negative. These fibers were accompanied by numerous highly varicose, purely catecholaminergic fibers suggesting local neurotransmitter interaction. The perivascular plexus contained Ang-positive, mostly non-varicose, and numerous exclusively TH-positive and Ang-positive fibers co-localized Ang and TH. Subendocardial Ang-positive fibers were mainly non-varicose and TH-negative except for clusters of (1) highly varicose tortuous or spouting fibers, or (2) groupings of thin, palisade-forming fibers that resembledafferent terminals. Tissue Ang I and Ang II concentrations were 6.2 ± 2.6 and 156.4 ± 174.1, Ang III-V concentrations <2.9 fmo/l.

Conclusions: Angiotensin fibers innervate the human right atrium and are catecholaminergic or non-catecholaminergic (probably afferent or parasympathetic). Intracardiac neuronal Ang II-release may contribute to atrial Ang concentrations and may reset atrial autonomic baroreceptor reflexes via synaptic Ang receptors to control blood pressure.
40 years. Pulverized brand-names and generics containing either amlodipine or candesartan did not differ with respect to their taste acceptability.

**Conclusions:** The taste of medicines is a crucial modulator of medication adherence in childhood, especially in asymptomatic conditions like hypertension. Future guidelines for the management of childhood hypertension should recognize the role of taste acceptability when deciding which medicine to prescribe to a child with hypertension.

---

**Impact of uninephrectomy on body L-arginine homeostasis and blood pressure control (NCCR project)**

Samyuktha Pillai1, Ralph Fingerhut2, François Verrey3

1University of Zurich, Institute of Physiology; 2Kinderspital Zurich

L-arginine plays an important role as precursor for a variety of physiologically important substances including citrulline, urea, ornithine, proline and nitric oxide, and the kidney is a major site for its metabolism. Uninephrectomy (UNX) is observed to cause an increase in the size of the remnant kidney and, to some degree, compensation of the glomerular filtration rate. As very little is known about UNX-induced effects on blood pressure control and expression levels of transporters and enzymes involved in arginine metabolism, we are using mice to test the hypothesis that renal mass reduction impacts on Arg metabolism and possibly thereby affects blood pressure control. C57/B6 female and male mice were subjected to left UNX or sham operated. Blood pressure was measured using a tail-cuff system and verified by telemetry. The concentrations of plasma amino acids and other parameters were analyzed.

Our results show that mice having undergone UNX display an increased systolic blood pressure (120 ± 2.14 mm Hg by tail cuff measurements, n = 9-18). This effect was more pronounced in females than males and observed also by telemetry. Plasma levels of asymmetric dimethyl arginine (ADMA), an inhibitor of NOS considered to be a good marker for renal disease, were increased in UNX animals, whereas the level of none of the proteinogenic amino acids was changed significantly. There were also no changes in the mRNA expression levels of Arg transporters and enzymes involved in arginine metabolism. The amount of urinary nitrate and nitrite was unchanged indicating that the observed changes in blood pressure were probably not mediated by changes in the NO levels. Our observations suggest that UNX affects blood pressure and the effects are less pronounced in males, possibly due to a more important remnant kidney compensatory growth.
Platelet-derived growth factor receptor β (PDGFRβ) expression in human peritoneum
Harald Seeger1, Nikol Braun1, Joerg Latuse1, M. Dominik Alschner1, Peter Fritz1, Ilka Edenhofer1, Dagmar Biegger1, Maja Lindemeyer1, Rudolf P. Wuthrich1, Stephan Seeger1  
1Division of Nephrology, Hospital, Zurich; 2Division of General Internal Medicine and Nephrology, Robert-Bosch-Hospital, Stuttgart, Germany; 3Division of Pathology, Robert-Bosch-Hospital, Stuttgart, Germany; 4Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany; 5Institute of Physiology, University of Zurich, Switzerland

Introduction: Simple peritoneal fibrosis and encapsulating peritoneal sclerosis (EPS) are important lesions in the peritoneum of patients on peritoneal dialysis (PD). We previously described a population of podoplanin positive myofibroblasts in peritoneal biopsies from patients with EPS. PDGFR receptor β (PDGFRβ) is a marker of pericytes and PDGFs might be involved in the fibrotic response of the peritoneum. This study aimed to describe PDGFRβ in the human peritoneum.

Methods: In this retrospective analysis we used immunostained PDGFRβ in peritoneal biopsies from patients with EPS (n = 6), on PD without signs of EPS (n = 5), and compared them with normal peritoneum (n = 4) and peritoneum from uremic patients (n = 5). Consecutive sections were stained for smooth-muscle actin (SMA) and podoplanin. Slides were scored semiquantitatively by two observers blinded to the diagnosis.

Results: PDGFRβ was expressed by cells of arterial walls in all biopsies. A prominent population of PDGFRβ positive cells was present in the normal peritoneum, which were SMA negative on consecutive sections. In patients on PD a high number of PDGFRβ was also positive for SMA. In EPS the majority of podoplanin positive cells were positive for PDGFRβ. In peritoneal biopsies from normal and uremic patients the expression of SMA was mainly restricted to cells of arterial walls. Podoplanin expression was restricted to lymphatic vessels in normal peritoneum, in uremic patients, and patients on EPS.

Conclusions: As podoplanin positive myofibroblasts express PDGFRβ, these cells might be related to pericytes (rather than other sources of fibroblasts). PDGFRβ might turn out to be a therapeutic target in EPS.

Assessment of lean tissue mass (LTM) in maintenance hemodialysis (HD) patients
Rebecca Winzeler1, Hans-Rudolf Rätz2, Denes Kiss2, Thomas Kistler2, Agnes Kneubüh1, Johannes Trachsel3, Marco Miozzari4, Patrice Ambühl1  
1Stadtpital Waid, Zürich; 2Kantonsspital Baden; 3Kantonsspital Basel; 4Kantonsspital Winterthur; 5Spital Lachen; 6Kantonsspital Schaffhausen

Background: Physical capacity, and, therefore, muscle mass, is an important predictor for survival in maintenance HD patients. Bioelectrical impedance analysis (BIA) is a simple, noninvasive method to assess body composition. The aim of the present study was to analyze LTM and its longitudinal change in the Swiss HD population.

Methods: 427 patients were evaluated from the monitorI project, a prospective dynamic hemodialysis cohort assessing a wide range of medical data. LTM, which provides information on the patients muscle mass, was analyzed by BIA measurement once a year over 3 years.

Results: Mean score for LTM was 44.8%, indicating a very low portion of muscle mass. LTM was analyzed after stratification for age, diagnosis vintage and Charlson Comorbidity Index (CCI) (table).

Patients with high initial LTM tend to have a steep decline in follow-up measurements (>5%) regardless of age, sex, dialysis vintage and CCI. The majority of patients have stable LTM over the observation period.

Conclusions: Patients on maintenance HD present with severe reduction in LTM compared to healthy individuals, reflecting sarcopenia to be a serious problem in this population. However, LTM seems to stabilize over time, especially in patients in the lower LTM range. As sarcopenia is associated with higher mortality and limited functional independency, efforts should be made towards improving muscle mass in HD patients.

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>≤39 yrs</th>
<th>≤39 yrs</th>
<th>40–59 yrs</th>
<th>40–59 yrs</th>
<th>60–79 yrs</th>
<th>60–79 yrs</th>
<th>≥80 yrs</th>
<th>≥80 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
</tr>
<tr>
<td>LTM (%)</td>
<td>59.8 ± 12.3</td>
<td>50.9 ± 14.6</td>
<td>42.0 ± 11.9</td>
<td>42.5 ± 9.1</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
</tr>
<tr>
<td>LTM (%)</td>
<td>47.1 ± 12.5</td>
<td>44.6 ± 13.8</td>
<td>43.2 ± 12.0</td>
<td>42.8 ± 11.8</td>
<td>0.081</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCI</td>
<td>low</td>
<td>average</td>
<td>high</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
</tr>
<tr>
<td>LTM (%)</td>
<td>47.4 ± 13.7</td>
<td>43.3 ± 12.0</td>
<td>41.0 ± 10.8</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Compared to patients from the ERA-EDTA registry (2012), patients in our analysis from Switzerland have a lower mortality despite being older. Our data indicate an inverse correlation of patient survival with dialysis vintage independent of age. A more comprehensive picture will result from the Swiss dialysis registry collections.

Handgrip strength and mortality in a hemodialysis (HD) cohort
Rebecca Winzeler1, Hans-Rudolf Rätz2, Denes Kiss3, Thomas Kistler2, Agnes Kneubüh1, Johannes Trachsel6, Marco Miozzari4, Patrice Ambühl1  
1Stadtpital Waid, Zürich; 2Kantonsspital Baden; 3Kantonsspital Basel; 4Kantonsspital Winterthur; 5Spital Lachen; 6Kantonsspital Schaffhausen

Background: Poor muscular strength has been shown to be associated with increased mortality in healthy people. The aim of this study was to assess muscular strength, its longitudinal change, and its association with mortality in a Swiss HD cohort.

Methods: 340 patients were evaluated from the monitorI project, a prospective dynamic hemodialysis cohort assessing a wide range of clinical, laboratory and anthropometrical data. Muscular strength was measured using a handgrip dynamometer.

Results: Mean handgrip strength was 22.3 kg (male: 26.4 kg, female: 16.5 kg), which is significantly lower compared to age-matched healthy individuals.

With every additional kilogram of handgrip strength (adjusted for age, sex, CCI and time on HD), patients probability to die is reduced by 4% (95% C.I.: 0.929–0.993). Patients with an increase in absolute handgrip strength have a significantly better survival compared to individuals with decreased handgrip.

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>≤1 year</th>
<th>&gt;1 year</th>
<th>≤3 yrs</th>
<th>&gt;3 yrs</th>
<th>≤8 yrs</th>
<th>&gt;8 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
</tr>
<tr>
<td>LTM (%)</td>
<td>47.1 ± 12.5</td>
<td>44.6 ± 13.8</td>
<td>43.2 ± 12.0</td>
<td>42.8 ± 11.8</td>
<td>0.081</td>
<td></td>
</tr>
<tr>
<td>CCI</td>
<td>low</td>
<td>average</td>
<td>high</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
</tr>
<tr>
<td>LTM (%)</td>
<td>47.4 ± 13.7</td>
<td>43.3 ± 12.0</td>
<td>41.0 ± 10.8</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions: Patients on maintenance HD present with severe reduction in muscle strength compared to healthy individuals. As muscular strength is associated with mortality, measures should be taken to improve muscle capacity in HD patients. An interventional study would be necessary to prove causal relation with mortality.

<table>
<thead>
<tr>
<th>Handgrip strength (kg)</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>CCI</th>
<th>Time on HD (years)</th>
<th>LTM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (N = 126)</td>
<td>71.6 ± 13.3</td>
<td>69.8 ± 15.6</td>
<td>4.0 ± 1.8</td>
<td>4.3 ± 5.5</td>
<td>41.7 ± 12.8</td>
</tr>
<tr>
<td>Average (N = 101)</td>
<td>70.0 ± 12.8</td>
<td>75.4 ± 15.4</td>
<td>4.4 ± 2.0</td>
<td>3.3 ± 4.6</td>
<td>42.0 ± 12.2</td>
</tr>
<tr>
<td>High (N = 113)</td>
<td>63.2 ± 16.4</td>
<td>80.0 ± 14.3</td>
<td>3.9 ± 2.0</td>
<td>3.2 ± 3.8</td>
<td>50.1 ± 12.7</td>
</tr>
</tbody>
</table>

*) P <0.001 vs. "low handgrip strength" **) P <0.001 vs. "average handgrip strength" **) Charlson Comorbidity Index

Is the nutritional risk screening (NRS) score a useful tool to predict changes in lean tissue mass of maintenance hemodialysis (HD) patients?

Rebecca Winzeler, Hans-Rudolf Rätz, Denes Kiss, Thomas Kißler, Agnes Kneubühl, Johannes Trachslifer, Marco Mazzetta, Patrice Ambühl

1) Stadtpital Waid, Zürich; 2) Kantons spitale Baden; 3) Kantons spitale Baselland, Liestal; 4) Kantons spitale Winterthur; 5) Spital Lachen; 6) Kantons spitale Schaffhausen

Background: Impaired nutritional status is frequent in hemodialysis (HD) patients. The aim of the present study was to evaluate the prognostic usefulness of the NRS score to predict a change in lean tissue mass (LTM) in HD patients dialyzed in Switzerland.

Methods: 375 patients were evaluated from the monitor! project, a prospective dynamic hemodialysis cohort assessing a wide range of clinical, laboratory and anthropometrical data. Nutritional risk was assessed by the NRS questionnaire. Lean tissue mass, serving as a proxy for muscle mass, was analyzed by bioelectrical impedance analysis (BIA) measurement. NRS scores were correlated with occurrence of LTM changes within 1 year.

Results: Mean LTM was 42.8%, indicating very low muscle mass. Stratification of the study population according to direction of LTM change (decline, none, increase) revealed no relevant association with comorbidity and age, but patients with an increase in LTM are significantly longer on HD.

Comparison of sodium conductivity prescription and dialysate sodium concentration with three different hemodialysis (HD) monitors: not all the monitors are equal

Eric Descombes, Benoit Fellay, Erwin Riedo, Ould Maouloud Hemetti, Jean-Luc Magnin, Gilbert Fellay

1) Service of Nephrology, HFR Fribourg Hôpital Cantonal, Fribourg, Switzerland; 2) Central Laboratory, HFR Fribourg Hôpital Cantonal, Fribourg, Switzerland

Background: Individualized sodium prescription and/or sodium modeling have been proposed to improve tolerance to HD, improve blood pressure control or optimize sodium balance. For this purpose it is of course necessary to accurately know if the sodium concentration in the inlet dialysate [iNa] corresponds to what is prescribed. The aim of the present study was to compare on 3 different HD monitors the sodium conductivity prescribed with the measured values of [iNa].

Methods: In our center we use the following monitors: Gambro AK200, Nikkiso DBB-05/07 and Fresenius 5008. During 79 HD an aliquot of dialysate was drawn from the inlet line two times during the session and the conductivity prescribed at the moment of drawing was recorded. The [iNa] was then measured by the indirect ISE method with a COBAS 6000 (Roche). Finally, the prescribed and measured values were compared for each type of monitor.

Results: 178 inlet dialysate specimens were analyzed and the main results are reported in table 1. With all monitors the mean measured [iNa] was higher than the prescribed values. However, while with the Nikkiso and Fresenius monitors the mean difference was rather small (plus 0.56 and 0.70 mmol/l), with the Gambro AK200 it was much higher (+3.5 mmol/l). Passing&Bablok analysis shows that the dispersion of the individual [iNa] values is also different for the 3 monitors.

Conclusions: The present data show that for a same prescription not all the dialysis monitors deliver the same dialysate concentration of sodium, certainly due to difference in the algorithms and/or procedures used to prepare the dialysate. This discordance may explain some differences in the dialysis tolerance observed when a patient is dialyzed using a different monitor than the usual one.

Therefore clinicians should pay attention to this point when prescribing sodium conductivity and/or sodium modeling on different HD monitors.

Table 1.

<table>
<thead>
<tr>
<th>Dialysis monitor</th>
<th>Prescribed Na conductivity</th>
<th>Measured sodium concentration</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmol/l-equivalent</td>
<td>mmol/l</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Gambro AK200</td>
<td>n=49</td>
<td>139.49 ± 2.92</td>
<td>143.02 ± 3.98</td>
</tr>
<tr>
<td>Nikkiso DBB-05/07</td>
<td>n=62</td>
<td>139.81 ± 2.53</td>
<td>140.37 ± 2.73</td>
</tr>
<tr>
<td>Fresenius 5008</td>
<td>n=47</td>
<td>138.49 ± 3.39</td>
<td>139.13 ± 4.08</td>
</tr>
</tbody>
</table>

The predictive power of an NRS score ≥2 for a substantial decline in muscle mass (≥10%) was calculated to have a sensitivity of 78%, and a specificity of 35%. In contrast, an NRS score of 1 has a negative predictive value (NPV) of 94% for severe muscle loss. An analog analysis was performed with hand grip strength instead of muscle mass, giving similar results.

Conclusions: Assessment of maintenance HD patients by NRS can be used as a straightforward and accurate tool to identify subjects with negligible risk for substantial muscle loss. However, the screening instrument is unsuitable to detect patients developing sarcopenia within 1 year’s time. No correlation was found for changes in muscle mass and survival, which may be explained by the short follow-up.

Baclofen toxicity in a dialysis patient

Theodora Fragkou, Konstantina Goula, Ourania Drakoulougkona

“St Andrews” General State Hospital, Patras, Greece

Background: Baclofen, a derivative of γ-aminobutyric acid, is an oral antispasmodic used to treat spasticity of spinal origin. It is eliminated predominantly by the kidneys and patients with impaired renal function are at particular risk for baclofen accumulation. Many investigators suggest that haemodialysis is a reasonable treatment modality in patients with overdose even in patients with normal renal function. We present a case of a dialysis patient who developed unconsciousness after receiving baclofen and was relieved of symptoms after dialysis treatment.

Case: A 70-year old man on dialysis was admitted to our hospital due to loss of consciousness. His sister reported that he had been started on baclofen treatment due to leg muscle pain, two days ago. He had totally received 40 mg of baclofen. On clinical examination, his temperature was 37.5 °C; blood pressure 110/70 mm Hg; he was disorientated in a state of confusion, GCS 7, without signs of localization. Laboratory tests showed Hb 15 g/dl, leukocytes 8090/μl, platelets 154000/μl, potassium 5.4 meq/l, sodium 134 meq/l, urea 190 mg/dl, creatinine 10.3 mg/dl, SGOT 12 IU/l, SGPT 28 IU/l. Brain computed tomography did not show acute findings. Haemodialysis was performed and the patient showed clinical improvement. Complete recovery was achieved after two dialysis sessions.

Discussion: Baclofen is a drug, 80% of which, is excreted unchanged by glomerular filtration. Since it is a small molecule, it has a low volume of distribution and low protein binding, dialysis treatment is effective in removing it. In ESRD patients such as our patient was, even low doses can cause serious toxicity. There are a few cases of baclofen toxicity in these patients reported in the literature. Further studies should elucidate if the administration of baclofen in these patients is appropriate.
The association between ultrafiltration volume and difference of the pre- and post-dialysis hemoglobin levels in maintenance hemodialysis patients

Michael Moeddel
Klinik Im Park, Zürich

Background: The question whether a greater ultrafiltration volume will cause higher hemoglobin/hematocrit levels or not is discussed controversially (1). Aim of the study is to examine the association between ultrafiltration volume and changes in hemoglobin levels during hemodialysis in maintenance hemodialysis patients.

Methods: A multicentre, retrospective/prospective observational survey examining stable hemodialysis patients (n = 56) at the long interval (3d). The association between ultrafiltration volumes and the changes in hemoglobin levels were measured. Subgroups have been defined as diabetic, non-diabetic, low/medium ultrafiltration, low/ high weight patients. Treatment parameter illustrates patients in the participating dialysis units. Statistical analysis was performed by using Pearson’s correlation and 1-Student test.

Results: Pearson’s correlation:
Correlation between pre- and postdialytic hemoglobin level are for total patients and all subgroups highly positive (between 0.82 and 0.95) and each very significant (p <1%). T-test for paired samples: The differences between arithmetic means for pre- and postdialytic hemoglobin levels lies for total patients, diabetic and non-diabetic patient subgroups between –0.48 and –0.52 g/dl. They are very significant positive for all patients, non-diabetic patients (p <0.1% two-tailed) and significant for diabetic patients (p <5% two-tailed). Data in addition illustrate patients and treatment.

Conclusion: Our results revealed correlations between ultrafiltration volume and changes in intradialytic hemoglobin levels. The results demonstrate a post-dialysis hemoconcentration effect. The post-dialysis hemoconcentration seems to be larger in patients with high ultrafiltration and less with low ultrafiltration. Further studies are needed to quantify the complex relationship between hemoglobin and ultrafiltration volume. Anemia management in hemodialysis patients might be adapted to ultrafiltration volume.

Large variations in pulse wave velocity and reflection patterns occur during a hemodialysis session and are not related to the degree of ultrafiltration

Menno Pruim1, Daniel Teta1, Corina Rotaru2, Valentina Fomi Ogna1, Georges Halabi1, Bernard Waesberge, Michel Burnier1, Francois Feihl1
1Service of Nephrology and Hypertension, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; 2Internal Medicine, University Hospital Lausanne (CHUV), Hemodialysis Unit, Etablissements Hospitaliers du Nord Vaudois, Yverdon, Switzerland; 3Pathophysiology, University Hospital of Lausanne (CHUV), Lausanne, Switzerland

Background: Arteries of end-stage renal disease patients are characterized by accelerated atherosclerosis and chronically progressive arterial stiffening. The acute effect of hemodialysis sessions on arterial properties have been less intensively studied, with contradictory results, possibly due to lack of standardization. The aim of this study was therefore to assess arterial properties throughout a hemodialysis session performed under standardized conditions, and to compare patients dialyzed at stable body weight with those undergoing ultrafiltration.

Methods: carotid-radial (cr) and carotid-femoral (cf) Pulse wave velocity (PWV) and the central systolic augmentation index corrected for heart rate (Aix@75) were measured in 13 hemodialysis patients undergoing ultrafiltration (UF) and 8 patients dialyzed at stable body weight (SW). Measurements were taken just before, halfway through, and just after a standardized hemodialysis session.

Results: No significant differences were noted between the groups for Aix, PWV and their changes. When the arterial properties of both groups were analyzed together, median cr-PWV increased slightly (from 8.6 (8.0–9.4) to 9.9 m/sec (8.7–10.7) after hemodialysis, p = 0.09), cf-PWV did not (from 10.3 (8.8–13.1) to 10.1 m/sec (9.4–14.4), p = 0.7), and Aix@75 decreased significantly (from 28 (26.0–35) to 24.3% (20.8–32), p = 0.02). Large individual fluctuations occurred in arterial properties throughout hemodialysis in each group (see figure).

Conclusion: Independently of ultrafiltration, important changes in arterial wall properties occur during hemodialysis, which may partly account for the heterogeneous hemodynamic responses observed during dialysis sessions.

First experience in Switzerland of the HeRo® graft for arterio-venous access for hemodialysis

Sebastien Deglise1, Thomas Holzer2, Anne Cherpillod3, Sebastien Kissling4, Daniel Teta1, Francois Saucy1, Francesco Dorena1, Beat Von Albertini2, Jean-Marc Corpataux3
1Department of vascular Surgery, CHUV, Lausanne, Switzerland; 2Dialysis Center, Clinique Cecil, Lausanne, Switzerland; 3Department of Nephrology, CHUV, Lausanne, Switzerland; 4Department of Radiodiagnosis and Interventional Radiology, CHUV, Lausanne, Switzerland; 5Dialysis Center, Clinique Cecil, Lausanne, Switzerland

Background: Central vein stenosis or occlusion resulting from long term AV access or more often due to central venous catheters is one of the major causes of access failure in dialyzed patients. The initial approach is angioplasty with stent placement but low patency rates at 1 year have been reported. In these situations, creation of arterio-venous (AV) access on the lower limb or placement of long-term catheters is required, associated to poor outcomes, especially in term of infection. However, the use of a HeRo® graft seems to be a satisfactory alternative.

Method: The HeRo® Graft is a fully subcutaneous access system that bypasses central veins and differs from conventional graft since it has no venous anastomosis. It is composed of a 6 mm diameter ePTFE arterial graft that is attached to the brachial artery and tunneled to the deltoidpectoral groove. It is connected through a titanium connector to the venous component. This 5-mm diameter segment is made of radiopaque silicone with braided nitinol reinforcement and endovascularly placed to the right atrium.

Results: We report the case of a 54 year old man on hemodialysis for years due to diabetic nephropathy. He has a long history of failed native fistulas and prosthetic grafts on both arms. Due to bilateral
subclavian venous stenosis, it was decided to use the HeRO graft to avoid long-term catheter or lower limb access. The intervention was successful. At 6 months, the graft is used without the need of any re-intervention and with a flow of 1400 ml/min.

Conclusions: This is the first report in Switzerland of the use of the HeRO graft as AV access. Due to good patency rate at 2 years approaching 90% and reduced risk of infection compared with catheters, this graft seems to appear as an excellent solution in case of central vein stenosis.

Is supplementation of water soluble vitamins justified in chronic hemodialysis patients?

Thomas Hochgruber, Andreas Jehle, Michael Dickenmann, Theresa Klima
Clinic for Transplant Immunology and Nephrology, University Hospital Basel

Background: Deficiency of several water soluble vitamins has been reported in patients undergoing chronic hemodialysis (HD). Therefore in many dialysis centers vitamins are routinely supplemented. However no validated supplementation-strategy exists until now. We aimed to characterize the vitamin status in our dialysis population receiving 2 capsules of Dialvit® after each HD session.

Methods: We analyzed erythrocyte folic acid (EFA), vitamin B1 (V-B1) and Vitamin B6 (V-B6) plasma levels from blood drawn before a dialysis session in 100 patients undergoing chronic HD at the University Hospital of Basel.

Results: Mean values of EFA, VB-1 and VB-6 analyzed in 100 patients where 3182, 224 and 377 nmol/l respectively. In none of these patients serum vitamin levels were under the lower limit of normal, even in those not receiving vitamin supplementation (N = 11).

Conclusions: Based on our data dosage of 2 capsules of Dialvit® after each HD session may result in oversubstitution of these water soluble vitamins in many patients. As even patients without vitamin supplementation seem to have sufficient serum vitamin levels it is legitimate to question if general supplementation in HD patients is justified.

Sclerostin and other circulating bone remodeling markers in hemodialysis patients

Albina Nowak, Ferruh Artunc, Andreas Serra, Emily Pollock, Pierre-Alexandre Krayenbuhl, Christian Mueller, Björn Friedrich
1University Hospital Zurich, Division of Internal Medicine; 2University hospital of Tübingen, Germany; 3University Hospital Zurich, Division of Nephrology; 4Hospital Linth, Uznach, Switzerland; 5University hospital Basel, Division of Cardiology; 6Nephrology Center, Sindelfingen Leonberg Herrenberg, Germany

Background: Cardiovascular calcification contributes to the increased morbidity and mortality in hemodialysis patients. Sclerostin, an osteocyte-secreted protein, was recently identified as an antianabolic bone factor causing soft tissue calcification.

Methods: In our multicenter prospective longitudinal observational study following hemodialysis patients, we aimed to assess the associations of the circulating sclerostin and bone remodeling markers with long-term mortality. We also evaluated the relationship between circulating sclerostin, FGF23 and traditional remodeling markers.

Sclerostin levels in hemodialysis patients were compared with healthy controls.

Results: We enrolled 239 hemodialysis patients with a median follow up of 1191 [IQR 712-1232] days.

In Cox regression analysis, Fibroblast growth factor 23 (FGF23) (HR 1.44; 95%CI 1.14–1.83), parathyroid hormone (PTH) (HR 1.95; 95%CI 1.53–2.49) and alkaline phosphatase (AP) (HR 1.62; 95%CI 1.16–2.25) per SD, 25(OH)vitamin D (HR 0.32 (0.17–0.60) per natural log but not sclerostin (HR 0.97 95%CI 0.68–1.37) per SD increase levels were independently associated with mortality.

FGF23 (OR –0.06; 95%CI –0.14 to –0.02), PTH (OR –0.17; 95%CI –0.19 to –0.08) and AP (OR –0.17; 95%CI –0.19 to –0.08) were independently negatively associated with sclerostin levels after adjustments for possible confounders.

Among control and hemodialysis females, sclerostin levels were lower than in men (fig. 1).

Conclusion: FGF23, PTH, AP but not sclerostin levels predicted long-term mortality. Sclerostin was negatively associated with FGF23, PTH and AP and lower in female than in male subjects.

P 76

P 77
**Index of first authors**

<table>
<thead>
<tr>
<th>Ackermann D</th>
<th>27 S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aghagolzadeh P</td>
<td>4 S</td>
</tr>
<tr>
<td>Anderegg M</td>
<td>4 S</td>
</tr>
<tr>
<td>Arampatzis S</td>
<td>10 S, 22 S</td>
</tr>
<tr>
<td>Andelt P</td>
<td>22 S</td>
</tr>
<tr>
<td>Auberson M</td>
<td>21 S</td>
</tr>
<tr>
<td>Beck M</td>
<td>16 S</td>
</tr>
<tr>
<td>Berchtold L</td>
<td>22 S</td>
</tr>
<tr>
<td>Bohlender J</td>
<td>28 S</td>
</tr>
<tr>
<td>Bonani M</td>
<td>24 S</td>
</tr>
<tr>
<td>Boustou Y</td>
<td>22 S, 28 S, 31 S</td>
</tr>
<tr>
<td>Bucher C</td>
<td>15 S</td>
</tr>
<tr>
<td>Buchkremer F</td>
<td>15 S, 32 S</td>
</tr>
<tr>
<td>Chandak P</td>
<td>17 S</td>
</tr>
<tr>
<td>Chehade H</td>
<td>12 S</td>
</tr>
<tr>
<td>Cippà P</td>
<td>25 S</td>
</tr>
<tr>
<td>Daryadel A</td>
<td>7 S</td>
</tr>
<tr>
<td>Deglise S</td>
<td>32 S, 33 S</td>
</tr>
<tr>
<td>Descombes E</td>
<td>9 S, 31 S</td>
</tr>
<tr>
<td>Devetzis V</td>
<td>25 S</td>
</tr>
<tr>
<td>Dhayat N</td>
<td>7 S, 27 S</td>
</tr>
<tr>
<td>Eikrem Ø</td>
<td>3 S</td>
</tr>
<tr>
<td>Feraille E</td>
<td>6 S</td>
</tr>
<tr>
<td>Ferrier C</td>
<td>13 S</td>
</tr>
<tr>
<td>Fischer A</td>
<td>12 S</td>
</tr>
<tr>
<td>Forni Ogna V</td>
<td>8 S, 11 S, 13 S</td>
</tr>
<tr>
<td>Fraghkou T</td>
<td>31 S</td>
</tr>
<tr>
<td>Freudiger H</td>
<td>10 S</td>
</tr>
<tr>
<td>Georgalis A</td>
<td>25 S</td>
</tr>
<tr>
<td>Girsberger M</td>
<td>12 S, 16 S</td>
</tr>
<tr>
<td>Grebe SO</td>
<td>26 S</td>
</tr>
<tr>
<td>Grendelmeier I</td>
<td>15 S</td>
</tr>
<tr>
<td>Hemett O</td>
<td>14 S</td>
</tr>
<tr>
<td>Hess B</td>
<td>26 S</td>
</tr>
<tr>
<td>Hint-Minkowski P</td>
<td>26 S</td>
</tr>
<tr>
<td>Hlushchuk H</td>
<td>19 S</td>
</tr>
<tr>
<td>Hochgruber T</td>
<td>33 S</td>
</tr>
<tr>
<td>Hönger G</td>
<td>5 S</td>
</tr>
<tr>
<td>Hopfer H</td>
<td>2 S</td>
</tr>
<tr>
<td>Kalbermatten S</td>
<td>14 S</td>
</tr>
<tr>
<td>Kapoor S</td>
<td>3 S</td>
</tr>
<tr>
<td>Kitterer D</td>
<td>8 S</td>
</tr>
<tr>
<td>König K</td>
<td>11 S</td>
</tr>
<tr>
<td>Kosmidis M</td>
<td>17 S</td>
</tr>
<tr>
<td>Kürth J</td>
<td>6 S</td>
</tr>
<tr>
<td>Latus J</td>
<td>10 S, 29 S</td>
</tr>
<tr>
<td>Lava S</td>
<td>27, 28 S</td>
</tr>
<tr>
<td>Lister A</td>
<td>8 S</td>
</tr>
<tr>
<td>Luciani A</td>
<td>19 S</td>
</tr>
<tr>
<td>Martins F</td>
<td>9 S</td>
</tr>
<tr>
<td>Moeddel M</td>
<td>32 S</td>
</tr>
<tr>
<td>Monnard E</td>
<td>13 S</td>
</tr>
<tr>
<td>Moor M</td>
<td>20 S</td>
</tr>
<tr>
<td>Mordasini D</td>
<td>18 S</td>
</tr>
<tr>
<td>Mühlbacher F</td>
<td>23 S, 24 S</td>
</tr>
<tr>
<td>Nowak A</td>
<td>33 S</td>
</tr>
<tr>
<td>Ogna A</td>
<td>3 S, 13 S</td>
</tr>
<tr>
<td>Olinger E</td>
<td>2 S</td>
</tr>
<tr>
<td>Ould Maouloud Hemett</td>
<td>16 S</td>
</tr>
<tr>
<td>Pathare G</td>
<td>7 S</td>
</tr>
<tr>
<td>Pedrycz B</td>
<td>20 S</td>
</tr>
<tr>
<td>Pejcinovskii M</td>
<td>3 S</td>
</tr>
<tr>
<td>Pillai S</td>
<td>29 S</td>
</tr>
<tr>
<td>Pivin E</td>
<td>18 S</td>
</tr>
<tr>
<td>Ponte B</td>
<td>4 S</td>
</tr>
<tr>
<td>Pruijm M</td>
<td>32 S</td>
</tr>
<tr>
<td>Randi E</td>
<td>6 S</td>
</tr>
<tr>
<td>Riwanto M</td>
<td>19 S</td>
</tr>
<tr>
<td>Rodriguez D</td>
<td>19 S</td>
</tr>
<tr>
<td>Rudloff S</td>
<td>6 S</td>
</tr>
<tr>
<td>Schnyder A</td>
<td>5 S</td>
</tr>
<tr>
<td>Schumann A</td>
<td>20 S</td>
</tr>
<tr>
<td>Seeger H</td>
<td>25 S, 26 S, 30 S</td>
</tr>
<tr>
<td>Seleznik G</td>
<td>17 S</td>
</tr>
<tr>
<td>Shved N</td>
<td>18 S</td>
</tr>
<tr>
<td>Simforoosh A</td>
<td>10 S</td>
</tr>
<tr>
<td>Vakilzadeh N</td>
<td>17 S, 21 S</td>
</tr>
<tr>
<td>Vethe H</td>
<td>21 S</td>
</tr>
<tr>
<td>Vincenti F</td>
<td>4 S</td>
</tr>
<tr>
<td>Wallner J</td>
<td>29 S</td>
</tr>
<tr>
<td>Wehmeier C</td>
<td>14 S</td>
</tr>
<tr>
<td>Winzeler R</td>
<td>30 S, 31 S</td>
</tr>
<tr>
<td>Wnuk M</td>
<td>20 S</td>
</tr>
<tr>
<td>Zobrist M</td>
<td>16 S</td>
</tr>
</tbody>
</table>