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Targeting apoptosis to induce tolerance across memory T cell barriers

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Memory T cells represent a major barrier for tolerance induction in sensitized recipients and in large animals. The lack of effective strategies to inhibit memory T cell clonal expansion precludes the clinical translation of tolerance induction protocols based on costimulation blockade. We hypothesized that the pharmacological inhibition of essential anti-apoptotic factors in memory T cell generation and maintenance might represent a new strategy to deplete donor-reactive memory T cells.

The small-molecule Bcl-2/Bcl-xl inhibitor ABT-737 efficiently induced apoptosis in alloreactive memory T cells in vitro and in vivo. As a result, ABT-737 during- or long-term after priming markedly reduced the number of allospecific memory T cells in vivo. Thereby, skin graft survival was prolonged in sensitized mice by ABT-737-mediated control of the secondary immune response. Additionally, a short course of ABT-737 induction therapy was sufficient to overcome memory T cell-mediated resistance to costimulation blockade in a donor-specific transfusion model. Finally, we applied the same therapeutic approach to induce mixed chimerism and donor-specific tolerance across memory T cell barriers.

Since Bcl-2 inhibitors yielded encouraging safety results in clinical cancer trials, this novel approach might represent a substantial advance in the development of clinically applicable tolerance induction protocols.

Potential role of T cell and platelet microvesicles in mediating anti-thymocyte-globulin-induced hypercoagulobility in transplant patients

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Anti-thymocyte globulins (ATG) induce long-term immunosuppression in the setting of renal and hematopoietic stem cell transplantation by depletion of T cells. ATG causes hypercoagulability and thrombocytopenia. The mechanism underlying this phenomenon is unknown. One of the potential effector mechanisms of ATG is complement-mediated lysis of target cells. Antibody-tagged cells can escape lysis by shedding surface-derived microvesicles (MV) carrying C5b-9. MV were shown to have procoagulant properties in vitro, potentially linking MV release to hypercoagulobility.

We hypothesized that the extent of MV released into the blood stream following ATG infusion correlates with the degree of hypercoagulability and thrombocytopenia in patients. In an in vitro system, we found a fast and dose-dependent release of MV after incubation of either T cells or platelets with ATG in the presence of serum. These MV stained following ATG infusion correlates with the degree of hypercoagulability.

In conclusion, ATG induced the release of C5b-9-positive MV with procoagulant properties from T cells and platelets in vitro. In patients, ATG treatment resulted in thrombocytopenia, hypercoagulability and systemic complement activation. We are currently in the process of patient plasma MV analysis.

Impact of donor secretor status in ABO-incompatible living donor kidney transplantation

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Background: The ABO blood group is a major determinant in living donor kidney transplantation. However, the ABH-secretor status might also be involved in the early immunological response. Secretors have soluble ABH substance in their body fluids, including blood. In consequence, these antigens could neutralize circulating Anti-A- and/or B-antibodies in vivo. As renal tissue is also capable of producing soluble ABH-substance in secretors, we examined the influence of donor ABH-secretor status on outcome in ABO-incompatible living donor kidney transplantation.

Methods: We retrospectively analysed all patients who underwent ABO-incompatible kidney transplantation at the University Hospital Basel from September 2005 to August 2013 according to local protocol. The ABH-secretor status was determined either by molecular genetic analysis (n = 31) or serologically with Lewis b-antigen positivity indicating secretor status (n = 8).

Results: Of all 53 transplanted patients we excluded the first 8 patients, who underwent posttransplant immunoadsorption based on a fixed protocol, as well as six patients with either donor-specific HLA antibodies (n = 4) or with missing ABH-secretor-status (n = 3). Thirty patients were secretors and 9 non-secretors. The ABH-secretor status of the donor kidney had no significant influence on posttransplant anti-A and/or B-antibody titers, number of posttransplant immunoadsorptions and major short-term transplant outcomes.

Conclusions: Based on this small patient cohort the donor ABH-secretor status of the living donor has no influence on outcome in patients with ABO-incompatible living donor kidney transplantation. However, further studies with larger cohorts must be conducted and the influence of the ABH-secretor-status on long-term outcome has to be analysed.

Patient’s cooperation has a critical impact on kidney transplant waitlisting

J. Bruni, D. Tsinalis, I. Binet
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Kidney transplantation should be best performed early in suitable patients with ESRD. Waitlisting should thus occur as soon as the criteria are fulfilled even before renal replacement therapy (RRT) starts. However this is rarely the case and we investigated the reasons for delayed waitlisting.

Methods: All patients starting RRT at our center between 01.08.05 and 31.07.10 were analysed retrospectively regarding waitlisting status at RRT start, 6, 12 and 24 months later, if the patient was previously known to nephrology services (defined as <90d) and the reasons for not listing. Patient’s cooperation has a critical impact on kidney transplant waitlisting.

At T6, T12 and T24 the rate of suitable patients listed or transplanted in known vs. unknown patients was 73 vs 29% (p <0.01), 79 vs 62% (NS) and 84 vs 69% (NS). Among all patients, 75/158 had no medical contraindication for waitlisting, 21% deferred listing at a given time.

<table>
<thead>
<tr>
<th>Known</th>
<th>Unknown und FU&lt;90d</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>111</td>
</tr>
<tr>
<td>% males</td>
<td>66%</td>
</tr>
<tr>
<td>Age</td>
<td>60 ± 15</td>
</tr>
<tr>
<td>Listed within 2y</td>
<td>52.3% (58)</td>
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<tr>
<td>Months to listing</td>
<td>2.4 ± 16</td>
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*p <0.05, **p <0.001
Acute and six months mineral metabolism adaptation in living kidney donors: a prospective study

Sophie M. De Seigneux, Belen Ponte, Andrea Trombetti, Thomas Emandez, Karine Hadaya and Pierre-Yves F. Martin
University Hospital of Geneva

Background: Following the evolution of living kidney donors (LKD) is important to understand renal adaptation to renal mass reduction. In this prospective study, we follow mineral metabolism adaptation of LKD’s over six months.

Methods: From May 2010 to December 2012, we included and followed 26 adults LKD’s. Their mineral parameters including regulatory hormones and renal function were repeatedly measured at day 0, 1, 2 and 3, and 6 months after donation.

Results: After nephrectomy, donors presented transient hypocalcemia and secondary hyperparathyroidism. Both circulating FGF23 and α-Klotho decreased during the first post-operative days and FGF23 decline was positively correlated to hypocalcemia. At 6 months after donation, donors had lower eGFR and 1,25(OH)2D3 compared to predonation levels, whereas 25(OH)D3 was unchanged. PTH levels increased at 6 months. Hormonal changes were associated with decreased plasma phosphate levels and renal tubular reabsorption of phosphate. In comparison to pre-donation, circulating FGF23 levels were unchanged whereas α-Klotho levels were lower.

Conclusions: Six months after kidney donation, donors developed a secondary hyperparathyroidism and lower phosphate levels probably related to 1,25(OH)2D3 deficiency. FGF23 levels did not rise in this specific population, whereas α-Klotho levels were only slightly decreased compared to predonation levels. This observation indicates that changes in renal phosphate handling are independent of FGF23 in LKD’s. This may in part explain their better cardiovascular prognosis.

Impact of proton-pump inhibitors and diuretics on the risk of hypomagnesemia in patients admitted to the emergency department

Spiros Arampatzis M.D.1,2, Gregor Lindner M.D.1,2, Georg-Christian Funk M.D.1,2, Alexander Benedikt Leichtle M.D.1,2, Georg-Martin Friedler M.D.1,2, Andreas Pasch M.D.1,2, Markus Mohaupt M.D.1,2, Aristomenis Exadaktylos M.D.1,2
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Background: The aim of this study was to evaluate the risk of hypomagnesemia under concomitant use of proton pump inhibitors (PPIs) and diuretics and explore the role of hypomagnesemia as a risk factor for adverse outcome in a cohort of emergency department (ED) patients.

Methods: Cross-sectional study in 4,919 patients who presented to a large tertiary care ED between 01 January 2009 and 31 December 2010 with measurements of serum magnesium on admission. Hypomagnesemia was defined as serum magnesium concentration of <0.75 mmol/L. Demographic data, electrolyte disorders, data on medication, morbidities and outcome in terms of length of hospital stay and mortality were documented.

Results: The mean serum magnesium concentration was 0.81 mmol/L (SD 0.1); 1,195 patients (24%) showed hypomagnesemia on admission. Magnesium levels tended to be lower in patients under diuretic and PPI medication and were significantly lower in subjects taking both drugs (p <0.001). Use of loop diuretics (p = 0.002) and thiazide diuretics (p = 0.02) was a predictor for hypomagnesemia. In multivariable regression analyses, PPIs (OR 1.7, p <0.0001), diuretics (OR 1.3, p <0.011) and the presence of diabetes mellitus (OR 2.6, p <0.0001) were independently associated with hypomagnesemia. While mortality was not increased in patients with hypomagnesemia alone (p = 0.83), patients with concomitant hypokalemia had a significantly higher mortality rate (p = 0.03).

Conclusion: Hypomagnesemia is common in patients presenting to the ED and is associated with use of PPIs, diuretics, and the presence of diabetes. Hypomagnesemia with concomitant hypokalemia was an independent predictor of in-hospital mortality.

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Conclusion: Hypomagnesemia is common in patients presenting to the ED and is associated with use of PPIs, diuretics, and the presence of diabetes. Hypomagnesemia with concomitant hypokalemia was an independent predictor of in-hospital mortality.
Serum galactose-deficient IgA1 level changes depending on the degree of immunosuppression in IgA nephropathy patients after kidney transplantation

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An excess of poorly galactosylated IgA1 (Gd-IgA1) is known to be present both in the serum and in the glomerular immune deposits of patients with IgAN. Gd-IgA1 serves as an auto-antigen inducing the formation of auto-antibodies. In selected IgAN patients, immunosuppression (IS), most commonly corticosteroids (CS), has been shown to improve the clinical outcomes. It is unknown whether IS influences the serum levels of Gd-IgA1.

Single-centre retrospective observational study. The sera of IgAN patients were collected prior to kidney transplantation (t0) and at protocol biopsies 3 & 6 months post-transplant (t3 & t6). Patients were treated according to standard IS regimen, i.e. induction with basiliximab or thymoglobulin and triple IS with tacrolimus (FK), mycophenolate mofetil (MMF) and CS followed by tapering of CS.

Serum levels of IgA1 and Gd-IgA1 were measured by IgA1-specific ELISA and lectin-binding assay using N-acetyl galactosamine specific lectin Helix Aspersa (HAA), respectively.

Out of 64 IgAN patients treated with kidney transplantation between 2005 and 2012, 41 patients were eligible for the study. No patient was on IS at the time of the transplantation. Trough level of FK at 3 months of dose of 9.7 ± 2.7 and 7.4 ± 1.9 mg, respectively (p = 0.0117). The levels were significantly higher than at 6 months (9.8 ± 1.4 vs. 7.6 ± 2.0 ng/ml, p <0.0001). Trough level of MMF was not significantly different.

Thirty-five and 18 patients were on CS at 3 and 6 months with a daily dose of 9.7 ± 2.7 and 7.4 ± 1.9 mg, respectively (p = 0.0117). The levels were significantly higher than at 6 months (9.8 ± 1.4 vs. 7.6 ± 2.0 ng/ml, p <0.0001). Trough level of MMF was not significantly different.

Our results demonstrate that the serum levels of Gd-IgA1 can be reduced efficiently by IS. The therapeutic effect of IS in IgAN patients may be at least partly dependent on the decrease of serum Gd-IgA1.
Prevalence and predictors of sleep apnea in patients undergoing chronic intermittent hemodialysis

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Service de Néphrologie et Hypertension, CHUV, Lausanne, Switzerland;1-Centre d’Hémodialyse, Etablissements Hospitaliers du Nord Vaudois, Yverdon; 2-Centre d’Hémodialyse, Hôpital Intercantonal de la Broye, Payern; 1-Centre d’Hémodialyse, Clinique Cecil, Lausanne; 1 joint first authorship

Introduction: Sleep disordered breathing (SDB; including obstructive and central sleep apnea) is a common finding in ESRD patients undergoing intermittent hemodialysis (HD). Two recent studies reported a prevalence of 26 to 57% in USA. Our aim was to assess the prevalence of SBD in a Swiss HD population and to evaluate the predictive value of validated screening tools, HD characteristics and biometric parameters.

Methods: All patients attending six HD centers in Canton Vaud were screened. Eligible patients completed the Berlin questionnaire (BQ) and the Epworth Sleepiness Scale (ESS). Apnea-Hypopnea Index (AHI) was assessed by a home nocturnal polygraphy.

Results: 101 patients completed the study. 86% of them had a SDB (AHI >5/h): 22% had moderate (AHI 15–30/h) and 31% severe SDB (AHI >30/h). SBD had been previously diagnosed in 10% and was treated in 5% of patients.

Positive and negative predictive values of BQ were 58% and 47% respectively. 14.4% of the patients had excessive sleepiness (ESS >10/24).

In a univariate analysis, female gender, age, neck circumference, waist-to-hip ratio and time on renal replacement therapy (RRT) were associated with moderate to severe SBD, while BMI, eKT/V and weekly HD duration showed no association. Neck circumference (OR 1.31, p <0.01) and time on RRT (OR 1.21, p <0.01) were the only independent predictors of SBD in a multivariate analysis.

Conclusion: In the HD population we observed a high prevalence of SDB, which seems to be undertreated. Classical screening tools and risk factors are not useful to screen for SDB in HD patients. Neck circumference and time on RRT emerge as the best predictors of SBD in this population. Awareness of nephrologists to SBD should be increased to improve diagnosis of this corrigible cardiovascular risk factor.

Acknowledgements: This study was supported by grants of the Schweizerische Nierenstiftung and the Ligue Pulmonaire Vaudoise.

Intermittent hemodialysis reduces the severity of obstructive sleep apnea in patients with end stage renal disease by decreasing nocturnal rostral fluid shift

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Center for Investigation and Research in Sleep (CIRS) CHUV, Lausanne, Switzerland; 1-Département de Néphrologie et Hypertension, CHUV, Lausanne, Switzerland; 2-Center of Hemodialysis, EHNV, Yverdon, Switzerland: joint first authorship

Background: Obstructive sleep apnea (OSA) is more prevalent in end stage kidney disease (ESKD) patients than in the general population, and may participate to their increased cardiovascular morbidity. Recent observations suggest a role of overnight rostral fluid shift (ORFS, i.e. fluid displacement from the legs to the neck soft tissues) in the genesis of OSA in otherwise healthy subjects, in heart failure patients, and in hypertensive patients with venous insufficiency. We aimed to investigate the hypothesis that ORFS is linked to overhydration and influences the severity of OSA in ESKD patients on intermittent ambulatory hemodialysis (HD).

Methods: The severity of OSA was assessed during two consecutive attended polysomnographies (PSG), performed the night before and after an HD session and expressed as index of apneas and hypopneas per sleep hour (AHI). Total body overhydration and leg fluid volume were evaluated by bioimpedance.

Results: Data of 12 patients were available for this preliminary analysis. Mean (SD) AHI decreased significantly from pre-HD 59.7 (22.6) to post-HD 49.2 (20.2), p = 0.02. AHI was associated with the overhydration state (p = 0.02). Mean (SD) ORFS was 1’014 (695) ml pre-HD and 630 (507) ml post-HD (p <0.001). The reduction of ORFS from pre-HD to post-HD was associated with an improvement of AHI (p = 0.04).

Conclusions: There was a significant decrease in AHI between pre- and post-HD polysomnographies. Total body overhydration was significantly associated with the severity of OSA. Overnight rostral fluid shift seems to be a pathophysiologic mechanism contributing to the genesis of OSA in HD patients.

Acknowledgements: This study was supported by grants of the Schweizerische Nierenstiftung and the Ligue Pulmonaire Vaudoise.

Walking capacity improves survival in a large prospective Swiss dialysis cohort

Rebecca Winzeler1, Hans-Rudolf Rätz2, Denes Kiss2, Thomas Kistler3, Agnes Kneubüh4, Johannes Trachsel5, Marco Miczka2, Patrice Ambüh1, 1-Stadtspital Waad, Zürich; 2-Kantonsspital Baden; 3-Kantonsspital Liestal; 4-Kantonsspital Winterthur; 5-Spital Lachen; 6-Kantonsspital Schafthausen

Purpose: Previous studies revealed an association between physical activity and mortality in hemodialysis (HD) patients. The aim of this analysis was to assess the prognostic significance of walking distance on survival in a Swiss HD cohort.

Methods: The study population consists of 453 patients participating in the monitor project, a prospective dynamic multicentre HD cohort study. Physical capacity was measured by three-minute walk test (3MWT), upper body strength (UBS) with a handgrip dynamometer, and 24-hour step count with an armband motion detector (SenseWear®, Bodymedia). Patients were divided in 2 subgroups according to median of 3MWT. A multivar-iate analysis using Cox regression was performed.

Results: Mean scores for 3MWT, UBS and 24-hour step count were 158 ± 73 m, 23 ± 12 kg, and 3613 ± 3566 steps per day, respectively, indicating relevant impairment in overall physical fitness. Performing the same analysis stratified for UBS, significant differences are found for age, 3MWT and step count. The odds ratio for survival (adjusted for age, sex, CCI and time on HD) is 3.5 (95% C.I.: 12–9.8) for patients with high vs. low 3MWT (p = 0.018).

Conclusion: Patients with higher walking distance are significantly younger, healthier and spend less time in a hospital. In this cohort, walking distance, reflecting overall exercise capacity, is associated with better survival independ-ent of age, comorbidity and dialysis vintage.

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Conclusion: Patients with higher walking distance are significantly younger, healthier and spend less time in a hospital. In this cohort, walking distance, reflecting overall exercise capacity, is associated with better survival independ-ent of age, comorbidity and dialysis vintage.
**A multicentric prospective observational study analysing arterial stiffness in a hemodialysis cohort**

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**Background:** Chronic kidney disease (CKD), mainly as a result of medcal calcification, volume overload and endothelial dysfunction accelerates vascular stiffening related to age. Arterial stiffness is usually evaluated measuring the carotid-femoral pulse wave velocity (PWV). KDOQI Guidelines recommend monitoring pulse pressure (PP) as a surrogate for PWV. Both correlate to survival and incidence of cardiovascular disease. PWV can also be estimated by pulse wave analysis (PWA) obtained with an adapted sphygmonanometer on the brachial artery.

**Methods:** 29 stable hemodialysis patients underwent a midweek study dialysis in three consecutive weeks, defined as a 4 hour oHDF with blood flow, 800 ml/min, dialysate flow and 80 ml/min substitution rate. The dialyzer used was in randomized order a FX100, PF210F and CorDix, performed better than the two other dialyzers. Significant amounts of ß2M and lowers plasma leptin, with no relevant substitution rate. The dialyzer used was in randomized order a FX100, Polyflux 210H (PF210) or a FXCorDix100 (CorDix) dialyzer. Arterial samples were taken at oHDF start (t0), at 60 and 240 minutes (t60, t120) and 30 minutes after the end (t270). Blood side clearances were computed at 160 and t240 using pre- and post-dialyzer blood samples. Equilibrated removal ratios (eRR) were calculated from t0 and t270 samples. Dialysate obtained using a 1/25 split dialysate collector was assayed for ß2M, phosphate and albumin.

**Results** (mean ± SD): Elimination parameters for phosphate were similar in all three dialyzers. ß2M, phosphate and albumin.

**Conclusions:** oHDF with modern highflux dialyzers removes significant amounts of ß2M and lowers plasma leptin, with no relevant albumin loss. The CorDix dialyzer in these real-life conditions performed better than the two other dialyzers.

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**Efficient Removal of ß2-Microglobulin and Leptin by Online Hemodiafiltration: Comparison of Three State of the Art Dialyzers**

Beatrice Paul1, Andreas Buck1

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**Background:** This study compared three state-of-the-art highflux dialyzers with respect to the elimination by postdilution on-line HDF of leptin (18.6 kD), ß2-microglobulin (ß2M, 11.8 kD) and phosphate. Improved ß2M elimination should delay ß2M amyloidosis, and lowering leptin levels might improve nutritional status via increased appetite.

**Methods:** 29 stable hemodialysis patients underwent a midweek study dialysis in three consecutive weeks, defined as a 4 hour oHDF with 350 ml/min blood flow, 800 ml/min dialysate flow and 80 ml/min dialysate loss (19.2 L/4h)

**Results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PF210</th>
<th>FX100</th>
<th>CorDix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin eRR (%)</td>
<td>26.7 ± 23.0</td>
<td>39.2 ± 21.7</td>
<td>40.6 ± 27.5</td>
</tr>
<tr>
<td>Clearance 240 (ml/min)</td>
<td>89.7 ± 19.2</td>
<td>102.8 ± 20.4</td>
<td>110.8 ± 13.4</td>
</tr>
<tr>
<td>ß2M eRR (%)</td>
<td>62.7 ± 5.3</td>
<td>671 ± 5.0</td>
<td>72.3 ± 5.3</td>
</tr>
<tr>
<td>Clearance 240 (ml/min)</td>
<td>115.5 ± 9.8</td>
<td>136.3 ± 12.8</td>
<td>150.4 ± 10.9</td>
</tr>
<tr>
<td>Dialysate removal (mg/l h)</td>
<td>1910 ± 678</td>
<td>204.9 ± 62.4</td>
<td>215.1 ± 63.3</td>
</tr>
<tr>
<td>Albumin Dialysate loss (g/l h)</td>
<td>1.31 ± 0.12</td>
<td>2.10 ± 1.00</td>
<td>1.74 ± 1.01</td>
</tr>
</tbody>
</table>

* p < 0.001 vs. PF210 * p < 0.001 vs. FX100

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

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NHA2 is a recently cloned sodium/hydrogen exchanger present in all metazoan genomes with unknown biological function. Due to chromosomal localization, tissue distribution and inhibitor characteristics, NHA2 is believed to be the long sought sodium/thium countertransporter which was epidemiologically linked to the pathogenesis of diabetes mellitus and essential hypertension. We recently demonstrated 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 physiological role of NHA2 in the kidney we performed telemetric blood pressure measurements and metabolic balance studies in NHA2 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-OH Vitamin D3 levels remained unaltered. Interestingly, immunoblotting of kidney tissue lysates revealed significant differences in the expression of the thiazide-sensitive sodium/chloride co-transporter, mutated in Gitelman's syndrome, in the distal convoluted tubules of NHA2 KO mice.

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.

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**Oral communications – NCCR / experimental nephrology**

**OC 14**

**OC 15**

**OC 16**

**Oral communications – Dialysis**

**OC 14**

**OC 15**

**OC 16**
Urteric bud branching is suppressed by the loss of Trps1 due to the activation of TGF-β signaling
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We previously found that urteric bud branching is suppressed in the embryonic kidneys of Trps1-deficient (KO) mice. However, how Trps1 is involved in UB branching remains unknown. In the present study, we unveil the molecular mechanisms by which the loss of Trps1 suppresses UB branching. When we compared gene expression patterns via DNA microarray analysis using cultured urteric buds isolated from E11.5 kidneys of WT and KO embryos, we found aberrant expression of genes associated with the transforming growth factor (TGF)-β/Smad3 signaling pathway in the KO UBs. Western blot blot and immunohistochemistry analyses showed increased levels of β-catenin, KRE and phosphorylated Smad3 and decreased levels of Smurf2, Smad2, and c-Ski in the KO embryonic kidneys. In addition, TUNEL staining and immunohistochemical detection of PCNA revealed that the apoptosis of UB cells was upregulated and, conversely, that cell proliferation was suppressed. Finally, we demonstrated that the suppression of UB branching in the KO UBs was restored by the exogenous addition of the Smad3 inhibitor SIS3, indicating a critical role of Smad3 in the regulation of UB branching.}

The renal and systemic response to an acute phosphate load: evidence against the existence of a gut-derived regulatory mechanism in humans
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Phosphorus plasma concentrations is maintained within a narrow limits by the synergistic action of several hormones (PTH, FGF-23, klotho and 1,25 (OH)2D) which interact to create a complex system of positive and negative feedback. This complicated system of multiple interactions makes it difficult to predict the relative importance of these hormones and the temporal relation of their response in the elimination of a phosphate load in humans. In addition, a recent paper rose the issue of the existence of duodenal phosphate sensing mechanism responsible for the early elimination of phosphate by the gut. In this study we analyzed the hormonal response provoked by both intravenous and duodenal phosphate load in healthy human subjects. Furthermore, we investigated the existence of a gut-renal axis. Our results showed no difference in the phosphate elimination time-course between an oral versus an intravenous phosphate load thus ruling out the presence of an intestinal phosphate sensor. Furthermore, we were able to describe how the phosphate-related hormones react to a phosphate load and to better clarify the way they interplay.

Calciprotein particles induce an inflammatory response in macrophages
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Introduction: Calciprotein particles (CPP) are nanoscale mineral aggregates, which are commonly circulating in the blood of patients with chronic kidney disease (CKD). These particles contain amorphous (CPP-I) or crystalline (CPP-II) calcium phosphate along with the serum protein fetuin-A and albumin as their main constituents. We hypothesized that CPP might induce an inflammatory response in macrophages.
Methods: CPP-I and CPP-II were generated using phosphate- and calcium-enriched cell culture media along with FBS. Particles were identified by transmission electron microscopy (TEM). Mouse macrophage cell line RAW-264.7 was exposed to CPP-I or CPP-II in varying amounts for 24 hrs. Real time-PCR was performed for interleukin (IL)-6, IL-1β, IL-10 and tumor necrosis factor (TNF)α to determine the extent of inflammation induction.
Results: TEM data showed that CPP-I and CPP-II were amorphous spherical calcium phosphate in human and murine macrophages. CPP-I and CPP-II were smaller in size compared to CPP-II. When murine macrophage RAW-264.7 cells were exposed towards CPP-II, pro-inflammatory markers IL-6, IL-10 and TNF-α were upregulated. In contrast, IL-10 was unaffected by CPP-II exposure. Upon exposure towards CPP-I particles, no inflammatory response was elicited from RAW-264.7 cells.
Conclusion: These results indicate that CPP-II are pro-inflammatory particles. It is tempting to speculate that CPP-II might be involved in the induction and maintenance of the chronic inflammation.

Role of the Na/Ca exchanger NCX1 in osteoclasts: in vitro and in vivo studies
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Introduction: Bone is dissolved by a polarized cell, the osteoclast. Previous studies indicated that sodium/calcium exchanger (NCX) inhibitors decrease bone resorption in a dose dependent manner in vitro. In addition, siRNA-mediated knock-down of NCX1 significantly suppressed osteoclastic bone resorption in vitro, indicating a critical role of NCX1 in osteoclast-mediated bone resorption. To test the role of NCX1 in osteoclasts in vivo, we generated mice with osteoclast-specific deletion of NCX1.
Results: Mice with a floxed exon 11 of NCX1 were crossed with mice expressing Cre-recombinase under the influence of the cathespin K promoter to generate osteoclast-specific NCX1 knockout mice (herein named NCX1−/− mice). Osteoclasts differentiated from NCX1−/− mice displayed a 80% reduction of NCX1 mRNA and protein compared to wild-type mice. NCX2 was not expressed in osteoclasts. NCX3 was expressed a low levels in osteoclasts but was not upregulated in NCX1−/− osteoclasts. NCX1 expression was unaltered in extracellular tissues in NCX1−/− mice. Structural bone parameters, analyzed by high-resolution microcomputed tomography (μCT) were not different in 12 week old male and female wild-type and NCX1−/− mice. Similarly, no differences were observed when we assessed osteoclast differentiation or bone resorption in vitro of cells isolated from wild-type and NCX1−/− mice, respectively. Finally, to stimulate osteoclast-mediated bone resorption, we performed surgical ovariectomy in 12 week old female mice. Ovariectomy-induced bone loss, however, was identical in wild-type and NCX1−/− mice at 3, 6, 9 and 12 weeks after the operation.
Conclusion: Thus, our data indicate that genetically induced deficiency of NCX1 in osteoclasts does not affect osteoclast differentiation and bone resorption in vitro. Furthermore, osteoclast-specific deletion of NCX1 does not seem to affect bone volume in 12 week old mice or ovariectomy-induced bone loss in female mice until 12 weeks after the operation.

Calciprotein particles (CPP) are nanoscale mineral aggregates, which are commonly circulating in the blood of patients with chronic kidney disease (CKD). These particles contain amorphous (CPP-I) or crystalline (CPP-II) calcium phosphate along with the serum protein fetuin-A and albumin as their main constituents. We hypothesized that CPP might induce an inflammatory response in macrophages. CPP-I and CPP-II were generated using phosphate- and calcium-enriched cell culture media along with FBS. Particles were identified by transmission electron microscopy (TEM). Mouse macrophage cell line RAW-264.7 was exposed to CPP-I or CPP-II in varying amounts for 24 hrs. Real time-PCR was performed for interleukin (IL)-6, IL-1β, IL-10 and tumor necrosis factor (TNF)α to determine the extent of inflammation induced. TEM data showed that CPP-I and CPP-II were amorphous spherical calcium phosphate in human and murine macrophages. CPP-I and CPP-II were smaller in size compared to CPP-II. When murine macrophage RAW-264.7 cells were exposed towards CPP-II, pro-inflammatory markers IL-6, IL-10 and TNF-α were upregulated. In contrast, IL-10 was unaffected by CPP-II exposure. Upon exposure towards CPP-I particles, no inflammatory response was elicited from RAW-264.7 cells.

Conclusion: These results indicate that CPP-II are pro-inflammatory particles. It is tempting to speculate that CPP-II might be involved in the induction and maintenance of the chronic inflammation.
Socioeconomic effects of kidney transplantation

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Background: Kidney transplantation is the most successful therapy for end-stage renal disease. However there is virtually no data about its impact on the patient’s socioeconomic status in Switzerland.

Objectives: The aim of this study is to analyze the change in the socioeconomic status of patients after kidney transplantation.

Methods: Socioeconomic data of a historic cohort of patients, grafted within one year before and after kidney transplantation is collected and compared by means of t-tests, chi-square test and principle component analysis.

Results: So far 316 (218 men; 98 women), out of 535 (353 men; 182 women) addressed patients, have completed their questionnaire and signed written informed consent. The repliers are significantly older than the not-answering patients (unpaired t-test, p <0.05). No difference between answering and not-answering patients in either sex.

Conclusion: Preliminary results show that the great majority of renal transplanted patients (86%) declare improvement of life thanks to transplantation. As to the work status, transplantation does not seem to increase the total percentage of working patients. More precise evaluation is in progress.

P 03

Prevalence, etiology, therapy and implications of anemia after kidney Transplantation (PTA) in a large prospective Swiss transplant cohort

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Purpose: To study the prevalence and characteristics of PTA and its implications on graft function and patient survival in a Swiss transplant cohort.

Methods: Cross-sectional national survey among 5 Swiss transplant centers (Basel, Bern, Geneva, Lausanne and Zürich) with baseline and follow-up analyses in 2008 and 2012, respectively. Anemia status and treatment were associated with patient demographics, transplant characteristics and patient survival.

Results: 1019 patients (61% men). Mean age at baseline was 54 ± 13 years, with time since transplantation being 78 ± 73 months. Hemoglobin (Hb) was <11 g/dl in 20% of patients. Clinically meaningful differences were found between 2008 and 2012: Ferritin concentration was low, and supplementation with iron and folate/vitamin B12, and steroid treatment were less frequent in 2012. Mean ESA dosage and % of patients on ESA did not differ between 2008 and 2012. PTA.

Conclusion: PTA is common and probably not adequately treated in the Swiss transplant population. We identified GFR, ferritin and CRP to be predictors of PTA. In accordance with other investigations, we found PTA.
Background: Non-invasive biomarkers correlating with subclinical allograft rejection would be very useful to identify patients who should be further investigated by surveillance biopsies. Previously, we reported that urinary CXCL10 is a promising non-invasive biomarker for subclinical tubulo-interstitial inflammation, while it did not reflect vascular rejection (i.e., glomerulitis, endothelitis, and peritubular capillitis). The aim of this study was to investigate whether serum CXCL10 correlates with subclinical vascular rejection.

Methods: Retrospectively, 96 surveillance biopsies were selected and stratified according to the histology results to four groups as follows: (i) acute Banff scores zero (n = 30), (ii) infection group with acute Banff scores zero and tubulitis t1-3 (n = 18), (iii) tubulitis t1-3 (n = 18), and (iv) vascular rejection plus/minus tubulitis t1-3 (n = 32). Serum CXCL10 was measured by a sandwich ELISA.

Results: Median serum CXCL10 value of the vascular rejection group was significantly higher compared to the acute Banff scores zero and tubulitis t1-3 group (122 pg/ml vs. 76.2 pg/ml, and vs. 66.3 pg/ml; respectively; for both p = 0.02). Median serum CXCL10 level was as well significantly higher within the infection group compared to the acute Banff scores zero and tubulitis t1-3 group (143 pg/ml vs. 76.2 pg/ml, and vs. 66.3 pg/ml; p = 0.005 and p = 0.004, respectively).

Conclusion: In this pilot study, serum CXCL10 reflected subclinical vascular rejection however BKV or CMV infection confounded the results of CXCL measurement in the peripheral blood.
Correlation of serum and urinary matrix metalloproteases/ tissue inhibitors of metalloproteases with subclinical allograft fibrosis in renal transplantation

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Background: Progressive interstitial fibrosis and tubular atrophy (IF/TA) is a leading cause of chronic allograft dysfunction and is often related to tubulo-interstitial rejection. Increased extracellular matrix remodelling regulated by matrix metalloproteases (MMPs) and their inhibitors (TIMPs) has been implicated in the development of IF/TA.

Methods: We measured eight different MMPs/TIMPs in the urine and serum, and correlated their levels with IF/TA in surveillance biopsies obtained 3–6 months post-transplant.

Results: Only 1/8 serum MMPs/TIMPs (i.e. MMP-1) was significantly elevated in biopsies with IF/TA 2-3 (n = 10) compared to IF/TA 1 (n = 15), and normal histology (n = 15); p < 0.01. In addition, several serum and urinary MMPs/TIMPs were not different between biopsies demonstrating an early development of IF/TA (i.e. delta IF/TA ≥1 compared to a previous biopsy; n = 11) and stable grade of IF/TA (i.e. delta IF/TA = 0; n = 20). Next, we investigated whether serum and urinary MMPs/TIMPs levels are elevated during subclinical tubulitis (n = 25). Compared to biopsies with normal histology, 3/8 urinary MMPs/TIMPs levels (MMP-1, MMP-3, TIMP-1) were significantly higher during subclinical tubulitis; p <0.04.

Conclusion: These results indicate that serum and urinary MMPs/TIMPs do hardly correlate with existing or early developing IF/TA in surveillance biopsies. Furthermore, they suggest that extracellular matrix remodelling – reflected by elevated urinary MMPs/TIMPs – is most active during acute tubulo-interstitial inflammation.

Lithium poisoning at normal serum levels in a 70-year-old patient with acute kidney Failure

Julia Hennemann, Agnes Kneubühl, Thomas Bregenzer

Introduction: Renal complications of chronic Lithium intake include nephrogenic diabetes insipidus (NDI) and tubulointerstitial nephropathy (TIN). Acute intoxications may occur in suicide attempts, but also in dehydration and cause diarrhea, vomiting, arrhythmias and neurologic findings.

Case: A 70-year-old women, taking lithium for >30 years, presented with polydipsy, diarrhea, vomiting and unilateral arm tremor. Lithium level in the brain was >35%, and a lithium level of 1.01 mmol/L. For combined renal failure (NDI/TIN) she was intensively rehydrated. Polyuria extended up to 5000 ml/24h and diminished with neurologic recovery within 10 days.

Discussion: Lithium poisoning at therapeutic serum levels includes toxicity to the brain as well as with blood. Possible risk factors for lithium poisoning at therapeutic serum levels include age, neurologic comorbidity and simultaneous psychiatric medication. Impaired renal function may be an additional risk factor.

Mycobacterium Haemophilum – Cutaneous and Pulmonary Manifestation in a Renal Transplanted Patient

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Introduction: Mycobacterium haemophilum is a nontuberculous mycobacterium (NTM) which rarely causes localized or disseminated infections in immunocompromised hosts.

Case report: A 65-year-old patient with renal transplantaion in 1993 because of bilateral atrophic kidney presented with B-symptoms in severely reduced general condition. He was under immunosuppressive treatment with ciclosporin and mycophenolate and showed erythematous-violaceous nodules on the skin of the extremities, cheeks and sublingual and shortness of breath. Laboratory testing revealed stable GFR (CKD-EPI 32 ml/min/1.73 m2) and slightly increased CRP. Thoracic computertomography showed areas of ground glass appearance. Clinical and radiological findings forced to exclude systemic tuberculosis. Several sputum samples were PCR negative for Mycobacterium tuberculosis complex. Skin biopsy showed granulomatous inflammation (AFB) and no signs of relapse.

Discussion and conclusion: Diagnosis of NTM has to be considered in immunocompromised hosts. AFB may be NTM. And if PCR for M. tuberculosis complex is negative, specific PCR tests for NTM should be performed. There are no guidelines for the treatment of M. haemophilum. Antimicrobial resistance tests are not standardized. In our patient therapy with rifampin, clarithromycin and moxifloxacin was effective.

Digital necrosis and renal failure

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History: A 65- year-old man with a history of fatigue, weight loss and joint pain for two month was referred to our hospital. He suffered from Raynaud’s phenomenon in both hands. Five fingers showed signs of beginning digital necrosis. The patient developed renal failure.

Discussion: Digital necrosis may occur in a variety of conditions, but also in dehydration and cause diarrhea, vomiting, arrhythmias and neurologic findings.

Conclusion: Measurements of serum and urinary MMPs/TIMPs may help to identify patients at risk of digital necrosis.
with pulses of intravenous methylprednisolone and oral cyclophosphamide leading to an improvement of the kidney function, but no improvement of the lesions on the fingertips desite of the additional use of calcium channel blockers. Due to side effects we changed the treatment to intravenous pulses of cyclophosphamide, which we had to stop because of severe sepsis with staphylococcus aureus. After treating the sepsis we continued the treatment of the vasculitis with rituximab. Due to bacterial super infection debridement of the fingertips II, IV on the right hand and II, V on the left hand was necessary. After 2x1 gram of rituximab PR3-ANCA almost normalised and renal function recovered continuously.

Conclusion: Raynaud’s phenomenon and digital necrosis should include the differential diagnosis of ANCA associated vasculitis.

First Switzerland confirmed Case of Acute Kidney Injury associated with Metamizol Sodium therapy

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Metamizol is analgesic, anti-pyretic pyrazolone derivative, and non narcotic. Elimination is at 60% by kidney. Recently two unknown pain. The use as analgesic is controversial. Some countries (German, Switzerland, France...) allow its, and others prohibit its (USA, UK, Australia, Japan...) due to the side effects including fatal blood dyscrasias from aplastic anemia to agranulocytosis, and reversible non oliguric acute kidney injury (AKI). We report the first described case of Switzerland who developed an oligo-anuric acute renal failure after metamizol sodium ingestion.

It’s not Always Diabetic Nephropathy

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A 74 year old male patient with suspected diabetic nephropathy was referred to our outpatient clinic due to a rapid decline of kidney function over the past six months. Kidney function did not improve after stopping blood pressure medication. There was no history of NSAID or other drug intake. Urine analysis showed mixed glomerular and tubulointerstitial proteinuria with normal sediment. The serum and urine electrophoresis were normal. Because of the unexpected deterioration of kidney function and atypical proteinuria which did not fit to diabetic nephropathy alone, we performed a kidneiy biopsy which showed hypertensive nephropathy and, surprisingly, oxalate nephropathy. The past medical history revealed a gastroncoma due to a neuroendocrine carcinoma of the stomach. Later a diabetes mellitus developed. Oxalate biopsy confirmed atrophy of the pancreas. Gastroscopy revealed bacterial overgrowth. He was treated with Medronizod and we started substitution of pancreatic enzymes and citrate. Kidney function improved over the next few months.

Oxalate nephropathy occurs in context of massive intake, malabsorption syndrome (e.g. short bowel syndrome, inflammatory bowel disease and exocrine pancreas insufficiency), deficiency of degrading bacteria like in bacterial overgrowth of the bowel and urinary excretion of calciumoxalate following aethyglycol intoxication and massive overdose of vitamin c. In our patient pancreatic atrophy after gastrectomy in combination with bacterial overgrowth was the most likely cause for hyperoxaluria.

In conclusion any impairment of kidney function must be carefully evaluated also in a patient with Diabetes mellitus.

Renal failure associated with ureaplasma urealyticum ureteritis

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In May 2013, a 30 year old patient presented to our emergency unit because of severe, constant bilateral flank pain. The pain started two days ago, was accentuated at the end of urination, and did not respond to iboprofen. The patient felt febrile. In 2008, he had one episode of ureterolithiasis. Clinically there was tenderness on palpation in both flanks. The patient had 13.8 G/L leucocytes, a CRP level of 57 mg/l and a serum creatinine of 59 µmol/L. The urine showed 7 leucocytes /hp, one leucocyte cylinder, and no erythrocytes. There was no growth of bacteria in the urine culture. Because of persistent pain despite of tramadol, an abdominal CT was performed showing a periureteric stranding suggestive of a bilateral ureteritis. Because of a persistently elevated creatinine concentration, a kidney biopsy was performed and a therapy with prednisone at 80 mg (1 mg/kg) was started for suspected acute interstitial nephritis due to iboprofen. The biopsy showed normal kidney tissue; prednisone was tapered rapidly.

The creatinine level decreased to 144 µmol/l. As the flank pain remained severe and as a microhematuria developed, a urinary cytology (Cox-1 and Cox-2) was performed for ureaplasma, mycoplasma hominis and a PCR for neisseria gonorrhoe and chlamydia trachomatis were performed. There was growth of ureaplasma urealyticum (>10000 CFU/ml). A single dose of an antibiotic resulted in prompt release of symptoms. The creatinine value fell to 104 µmol/l reflecting a normal renal function in a muscular young man.

We report here a case of likely ureaplasma urealyticum ureteritis and concomitant renal failure. The findings suggest that it may not be a simple coincidence. We hypothesise that bilateral ureteritis led to transitory ureteric obstruction and renal failure.

Allele-specific human leucocyte antigen allomibody causing unexpected AMR after kidney graft transplantation

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A 44-year-old male patient suffering from end-stage renal failure due to FSGS underwent first living donor kidney transplantation. He had not received any blood transfusion in the past. Pre-transplant antibody crossmatch, while T- and B-cell CDC-crossmatch were negative. Due to the fact that only one very weak, allele-specific antibody was identified and no sensitizing event was recalled in the patient's history, this positive result was regarded as not clinically relevant. Therefore, the transplantation was considered being at low immunological risk and an induction treatment with an Il-2 antagonist and maintenance immunosuppression with tacrolimus/mycophenolate mofetil/stereoids was given. On day 5 post-transplant, allograft function failed to improve (serum creatinine 206 µmol/l, estimated target serum creatinine 140 µmol/l). Unexpectedly, allograft biopsy showed acute antibody-mediated rejection with acute tubular injury, peritubular capillaritis and diffuse C4d-positivity in peritubular capillaries. At the time-point of the biopsy, single antigen beads detected increased levels of donor-specific HLA-antibodies reacting with all HLA-A2 alleles (A*02:01: MFI 6400; A*02:03: MFI 2860; A*02:06: MFI 1861). The patient was immediately treated with a 7-day-course of antithymocyte globulin and steroids. Allograft function rapidly improved. This case report demonstrates that even very weak and supposedly allele-specific HLA-antibodies detected by single antigen bead analysis might be clinically relevant.
Successful treatment of a pacemaker infection with intraperitoneal daptomycin dosed according to systemic serum drug concentrations

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A 54-year-old female patient on long-term hemodialysis developed sepsis after insertion of a pacemaker for the treatment of symptomatic 3rd degree heart block. In four out of four blood culture bottles grew S. epidermidis sensitive to daptomycin (minimum inhibitory concentration 0.25 mcg/ml). Due to thrombomixes of the sural and superior vena cava, the pacemaker system could not be explanted and an extensive course of antibiotics was required. Intravenous daptomycin was commenced multiple times weekly. Hemodialysis was then switched to peritoneal dialysis due to venous dialysis access failure and daptomycin had to be administered intraperitoneally. Daptomycin is primarily renally excreted and only 15% is eliminated via hemodialysis and 11% by peritoneal dialysis so dose-reduction is required in these situations. Intraperitoneal daptomycin is usually only given to treat intraperitoneal infection with daptomycin-sensitive organisms. A single case-report in the literature suggested that therapeutic serum concentrations may however be achieved through intraperitoneal application. The graph below shows the daptomycin concentrations achieved through intravenous and then intraperitoneal application (denoted with a *). Administered doses in mcg are given on the graph. The blue rhombuses denote trough serum concentrations and the red squares the peak serum concentrations 4h after administration. Dose-adjustments were made to achieve a peak concentration/MIC ratio (Cmax/MIC) of approximately 150 (a ratio known in a mouse-model of S. aureus infection to be associated with 2 log killing) corresponding to a peak concentration (Cmax) of 40- 60 mcg/l and a trough concentration (Cmin) <24 mcg/l. Trough concentrations above 24 mcg/l (horizontal blue line on the graph) are known to be associated with increased muscle toxicity which is why this target Cmin of <24 mcg/l was set. Ultimately the patient could be successfully treated with 300 mcg daptomycin administered in 1000 ml of icodextrin with a dwell time of 12 hours intraperitoneally every 48 hours. Other than nausea which coincided with the highest peak daptomycin concentration of 160 mcg/l (see the graph below), the patient did not experience any daptomycin-related adverse effects. After a total of 4 weeks of daptomycin therapy the treatment was switched to rifampicin and fusidic acid per orally for another 10 weeks. After stop of the antibiotic treatment the control blood cultures remained negative.

Dose-adjustments were made to achieve a peak concentration/MIC ratio (Cmax/MIC) of approximately 150 (a ratio known in a mouse-model of S. aureus infection to be associated with 2 log killing) corresponding to a peak concentration (Cmax) of 40- 60 mcg/l and a trough concentration (Cmin) <24 mcg/l. Trough concentrations above 24 mcg/l (horizontal blue line on the graph) are known to be associated with increased muscle toxicity which is why this target Cmin of <24 mcg/l was set. Ultimately the patient could be successfully treated with 300 mcg daptomycin administered in 1000 ml of icodextrin with a dwell time of 12 hours intraperitoneally every 48 hours. Other than nausea which coincided with the highest peak daptomycin concentration of 160 mcg/l (see the graph below), the patient did not experience any daptomycin-related adverse effects. After a total of 4 weeks of daptomycin therapy the treatment was switched to rifampicin and fusidic acid per orally for another 10 weeks. After stop of the antibiotic treatment the control blood cultures remained negative.

C3 rapidly progressive glomerulonephritis as aHUS/CD46 mutation recurrence: graft loss 5 years after renal transplantation

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Atypical hemolytic uremic syndrome (aHUS) is caused by genetic abnormalities in the complement system leading to thrombocytopenia, hemolytic anemia, and acute kidney injury. Factor H mutations are found in the majority of patients with aHUS resulting in end-stage renal failure. The clinical course consists of high rates of disease recurrence after isolated kidney transplantation with a significant risk for graft loss. Perioperative plasma exchange to supplement factor H has been reported to prevent early graft dysfunction. We report a 29-year old woman who was diagnosed with aHUS. Sequencing of the CFH gene revealed two heterozygous mutations in the 3rd consensus repeat (4 c.720T>C, p.Ile216Thr) and 8 (c.1586T>G, p.Cys505Gly). She started. One month later, the patient resumed chronic dialysis. A new workup identified the at-risk CFH haplotype variant (a polymorphism present in 5% of the general population). The patient was transferred for post-transplant treatment. Identifying at risk SNP carriers may help to stratify recurrence risk and the use of prophylactic eculizumab.

PEG Interferon-Alfa 2A causing minimal change disease in a patient on hepatitis C Therapy

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Hepatitis C virus infection is one of the main causes of chronic liver disease worldwide. HCV infection is both a cause and complication of chronic kidney disease. The most common HCV related nephropathy is MPGN, usually in the context of Cryoglobulinaemia. Besides MPGN, other forms of glomerular disease have been associated with HCV infection, which include IgA nephropathy, post infectious glomerulonephritis, membranous nephropathy, thrombotic microangiopathies, focal and segmental glomerulosclerosis, and membranous glomerulopathy. Treatment with IFN is rarely associated with nephrotic syndrome and renal biopsy findings of minimal-change disease. We present a case report of Genotype 4 Hepatitis C infected Chinese man with base line HCV viral load of 491,915 IU/ml abnormal ALT/ AST, who developed nephrotic syndrome and renal biopsy/ electron microscopy proven minimal change disease after four months therapy with Peg interferon- alfa 2a and ribavirin. Serum albumin and proteinuria improved significantly after stopping treatment and oral prednisolone therapy. Either in chronically HCV-infected or in Peg interferon-alfa treated patients, renal functions should be monitored carefully. Although nephroticsy is rare, we emphasize that it can occur any time after the start of IFN therapy, and physicians treating patients with chronic hepatitis C must be aware of this potentially serious adverse event.

First Simultaneous Liver-Kidney Transplantation for Atypical Hemolytic Uremic Syndrome due to a Factor H double mutation

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Atypical hemolytic uremic syndrome (aHUS) is caused by genetic abnormalities in the complement system leading to thrombocytopenia, hemolytic anemia, and acute kidney injury. Factor H mutations are found in the majority of patients with aHUS resulting in end-stage renal failure. The clinical course consists of high rates of disease recurrence after isolated kidney transplantation with a significant risk for graft loss. Perioperative plasma exchange to supplement factor H has been reported to prevent early graft dysfunction. We report a 29-year old woman who was diagnosed with aHUS. Sequencing of the CFH gene revealed two heterozygous mutations in the 3rd consensus repeat (4 c.720T>C, p.Ile216Thr) and 8 (c.1586T>G, p.Cys505Gly). She developed end-stage renal failure in 2007. Six years after diagnosis, a simultaneous liver-kidney transplantation was performed. The immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil, and prednisone. Additionally, she received pre- and postoperatively plasma exchange and intraperatively plasma infusion during the anhepatic phase to provide functional factor H to prevent complement activation. The postoperative course was uneventful with immediate function of both grafts. Plasma exchange was performed daily in the first and bi-daily in the second week post-transplant. GFR, LDH and blood cell count remained normal. Currently, 8 months post-transplant there is no evidence for complement activation. To date, this is the first successful simultaneous liver-kidney transplantation for aHUS in Switzerland.
Eosinophilia in a Kidney Transplant Recipient with Allograft Failure

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We report a case of a 37-year-old woman presenting with allograft failure 12 years after the first kidney transplantation due to early recurrent focal segmental glomerulosclerosis. The patient returned on dialysis, and the immunosuppression regimen was tapered to a minimal maintenance therapy including 100 mg of cyclosporine and 12.5 mg of azathioprine daily.

Six weeks after starting the new immunosuppression, the patient complained of fever and a new onset of peripheral eosinophilia. At this time, white blood cell (WBC) count was 7900/µL with 7% eosinophils. A bone marrow examination was negative for lymphoma or leukemia, but showed an increased number of eosinophils (25% of total cells).

A renal biopsy was performed, and histology showed features characteristic of polyomavirus nephropathy, with focal segmental glomerulosclerosis, diffuse interstitial fibrosis, and arteritis with eosinophilic infiltrates. The patient was treated with a tapering course of prednisolone and cyclophosphamide, and eosinophilia eventually resolved with normalization of renal function.

Polyomavirus nephropathy caused by JCV in renal allograft recipients

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Introduction: The human polyomaviruses BK (BKV) and JC (JCV) are widely spread in the general population, where serologic evidence of past infection is found in 60–80%. They can cause significant disease, especially in immunocompromised hosts, and seem to have a better prognosis, but systematic studies are lacking.

Patients: A 35-year-old man was referred because of bilateral nephrocalcinosis, nephrolithiasis and CKD3A. One of his two nephropathies had had ESRD and underwent 2 renal transplants. Clinical workup revealed significant tubular proteinuria, mild aminoaciduria and hypophosphatemia with a reduced TmP/GFR. There was no glucosuria or acidemia. Mild hyperparathyroidism was explained by vitamin D deficiency and responded promptly to supplementation. There was no hypercalciuria, hypomagnesemia or hypokalemia.

Sequencing of the CLCN5 gene established the diagnosis of Dent’s disease. Sanger sequencing revealed a previously undescribed insertion of adenine following position 261 of the cDNA sequence (c.261_262insA) leading to substitution of glycine by arginine at amino acid position 88 with a frameshift and a stop signal at codon 97 (g.8887insA).

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Case 2: The patient’s brother had presented with acute hypokalemic paralysis at the age of 5. Severe rickets had been noted then and hypercalciuria, hyperphosphaturia, hyperaminoaciduria, glucosuria and isosthenuria were documented. Renal biopsy showed tubular atrophy with hyaline casts, interstitial fibrosis and nonspecific interstitial infiltrate. A dialysis of chronic interstitial nephritis with a Bartter-like syndrome was made.

Based on the brother’s diagnosis, we were – after 42 years including two periods of hemodialysis and two kidney transplantations – finally able to diagnose Dent’s disease.

Anti-GBM disease and the nephrotic syndrome

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Kantonsspital Aarau: Nephrologie, Zentrum für Labormedizin, Pathologie

Background: Anti-GBM disease usually manifests with a phenotype of rapidly progressive glomerulonephritis (RPGN), with or without pulmonary hemorrhage. Autoantibodies to the α3-chain of type IV collagen have been identified as pathogenic in this rare disease. We present a case where anti-GBM antibodies with a different specificity caused an entirely different clinical picture.

Case: This 88 year old patient was admitted with acute oliguric renal failure, uremic encephalopathy and the nephrotic syndrome. Dialysis treatment was initiated. Clinical workup revealed edema, nephrotic range unselective glomerular proteinuria (21 g/24h) and hypocalcemia. The urinary sediment did not show any dysmorphic erythrocytes or cell casts but slight lipiduria. Serologic examinations were negative for hepatitis B and C, HIV, ANA and ANCA. Complement C3 and C4 levels were normal. Serum electrophoresis showed a normal M-gradient with a normal free light chain kappa/lambda ratio. Abdominal fat biopsy was negative for amyloidosis.

The histologic findings of the renal biopsy displayed signs of membranoproliferative glomerulonephritis with crescents in two glomeruli upon light microscopy. Immunofluorescence was positive for IgG and C3 along the GBM but EM showed no deposits. The subsequently ordered anti-GBM antibodies were faintly positive in indirect immunofluorescence and in ELISA but negative in the chemiluminescence immunoassay (CIA) and line immunoassay LIA. While the former two use native kidney as targets, the latter both use recombinant α3(V)Ic1 antigen.

Conclusions: The anti-GBM antibodies in this case were not directed against the α3 chain of collagen IV but against some unknown α-chain collagen have been identified as pathogenic in this rare disease. We present a case where anti-GBM antibodies with a different specificity caused an entirely different clinical picture.

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Conclusions: The anti-GBM antibodies in this case were not directed against the α3 chain of collagen IV but against some unknown α-chain.
Osteoanabolic treatment for severe renal osteopathy after combined Kidney-Liver Transplantation: A case report

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Background: Chronic kidney disease is associated with the development of renal osteodystrophy (ROD) and characterized by abnormalities of bone turnover, mineralisation and volume. ROD is clinically associated with an increased prevalence of fractures. The effect of an osteoanabolic therapy with recombinant parathyroid hormone after combined kidney-liver transplantation has not been reported yet.

Case Presentation: A 42-y/o Caucasian male with hepatorenal syndrome underwent combined kidney liver transplantation in 2010. The patient had several riskfactors for fractures (alcohol abuse, cigarette smoking, hypothyroidism, sarcopenia, malnutrition, hypovitaminosis D and corticosteroid therapy) along with severely diminished bone mineral density (BMD, DXA-Scan, tab. 1) and suffered multiple fractures short after transplantation. Given the limitations of laboratory measurements (table 2) and DXA to assess bone disease in transplanted patients, a double tetracycline-labeled injection, is a potent anabolic agent and has been shown to be of benefit when treating dialysis patients with adynamic bone disease by increasing lumbar spine BMD and lowering serum phosphate (1).

Our patient showed an impressive improvement in BMD, bone turnover markers and bone biopsy indices after recombinant PTH therapy followed by an antiresorptive treatment, showing this treatment is also of clinical value after combined kidney-liver transplantation.

### Table 1

<table>
<thead>
<tr>
<th>Bone Density</th>
<th>DEXA 2010</th>
<th>DEXA 2012</th>
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<tr>
<td>LWS T Score (SD)</td>
<td>–3</td>
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<td>Schenkelhals T Score (SD)</td>
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<td>–2.5</td>
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<tr>
<td>Tibia Diaphase T Score (SD)</td>
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<td>–2.9</td>
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<tr>
<td>Tibia Epiphys T Score (SD)</td>
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<td>–3</td>
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<td>Radius T Score (SD)</td>
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### Table 2

<table>
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<th>Blood Results</th>
<th>March 2010</th>
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<th>August 2012</th>
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<td>PTH (15–65 pg/mL)</td>
<td>58</td>
<td>72</td>
<td>672</td>
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<tr>
<td>25-Hydroxy-Vit D3 (49–134 nmol/L)</td>
<td>50</td>
<td>40</td>
<td>63</td>
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<tr>
<td>1,25-Dihydroxy-Vit D3 (49–160 pmol/L)</td>
<td>&lt;12</td>
<td>47</td>
<td>32</td>
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<tr>
<td>Osteocalcin (&lt;42 ng/mL)</td>
<td>131.5</td>
<td>25.7</td>
<td></td>
</tr>
<tr>
<td>beta-CrossLaps (&lt;600 pg/mL)</td>
<td>1428</td>
<td>335</td>
<td></td>
</tr>
</tbody>
</table>

Urinary uromodulin as a marker of renal function and mass: data from a population-based study. Based study
Menno Pruijm, Michel Burnier, Belen Ponte, Daniel Ackermann, Fred Paccaud, Markus Mohaupt, Pierre-Yves Martin, Olivier Devuyst, Murielle Bochud

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Introduction: In genome-wide association studies, uromodulin (UMOD) locus, which encodes uromodulin, is associated with renal function and risk of chronic kidney disease, suggesting that uromodulin may be involved in pathways leading to renal function decline. Since uromodulin is exclusively produced by tubular cells lining the thick ascending limb of Henle, we hypothesized that urinary uromodulin might be a marker of renal function and mass. The aim of this study was to assess the relationship between ultrasound-measured renal dimensions and urinary uromodulin excretion rate (UER).

Methods: Blood sampling, a 24h urinary collection and renal ultrasound were performed in randomly selected adults from the population of Lausanne and Bern. UER was measured using a validated ELISA. Glomerular filtration rate was estimated with the CKD-EPI formula (eGFR) and measured by 24h creatinine clearance (mGFR). Subjects with renal cysts were excluded from the analysis.

Results: A total of 380 men and 437 women were included. Mean eGFR was slightly lower than mGFR (67.2 ± 20.9 ml/min/1.73 m² vs. 70.6 ± 20.6 ml/min/1.73 m², respectively; p <0.001). There was a positive association between the third caffeine tertile and fractional excretion of potassium in women (β = –0.08 mmol/l; p = 0.024), but not among men. This association was significant only for women taking the oral contraceptive pill (β = –0.13 mmol/l; p = 0.001). There was a positive association between plasma caffeine and fractional excretion of potassium in women (β = 0.04; p = 0.01). Overall, the prevalence of hypertension was significantly higher in CKD patients, if compared with patients with normal eGFR and ACR (p = 0.001). There was an inverse association between plasma potassium and the third caffeine tertile among women (p <0.001). There was a positive association between plasma potassium levels uniquely among women, suggesting that this association may be influenced by sex hormones.

Conclusion: We found an inverse association between plasma potassium and caffeine levels among women, suggesting that this association may be influenced by sex hormones.
Community-acquired Acute Kidney Injury: a prospective observational study

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Introduction: Acute Kidney Injury (AKI) is a major health problem and its diagnosis may be challenging. There is a paucity of data on AKI acquired in the community in westernized societies. We aimed to better define characteristics of AKI occurring within the community and the effectiveness of AKI initial management.

Methods: We undertook a prospective observational study within the Emergency Department of a University Hospital, screening for any patient >16 years admitted with an eGFR <60 ml/min and a rise in eGFR as compared to previous values, when available (KDIGO AKI criteria). Patients with chronic kidney disease (previously known for a eGFR <60 ml/min) and no acute rise from previous value were excluded. There was a daily identification of patients with the help of a computer-based database and all the cases with a eGFR <60 ml/min were subsequently reviewed by a panel of nephrologists.

Results: From May 1st to June 21st 2013, there were 8464 admissions in our Emergency Department, of which 325 patients (3.8%) had AKI. Mean age was 75 ± 15 years, and 60% were of male gender. AKI was unidentified in 52% of the cases. In the patients with AKI, mean eGFR and creatinine at admission were 36 ± 14 ml/min and 196 ± 172 μmol/L respectively. One third had superimposed AKI on CKD. Etiology of AKIs was prerenal (7%), renal (8%), postrenal (7%) and no clear cause was found in 9% of the cases. ICU admission and RRT were necessary in 10 and 3% of the patients respectively. 28-days mortality was 9.3%.

Conclusion: These preliminary results show that community-acquired AKI is underdiagnosed within the Emergency department. AKI is frequently found in the elderly, and the main etiology is prerenal. Though need of RRT is not frequent, 28-day mortality is still high in these patients.

Microhematuria in ADPKD

Division of Nephrology, USZ, Switzerland; Institute of Clinical Chemistry, USZ, Switzerland

Background: Clinical presentation in ADPKD is manifold and typically includes abdominal pain, nephrolithiasis [1], cyst infections and hematuria [2] in the advanced state of the disease. Gross Hematuria is associated with an increasing renal volume and hypertension and is reported to be a risk factor for an accelerated disease progression [3-7]. Microscopic hematuria rarely is reported in ADPKD patients and as it appears often asymptomatic it is mostly discovered as part of a routine examination. In the present study we investigate the occurrence of microscopic non glomerular hematuria and its association with clinical risk factors.

Methods: Data of 175 patients enrolled in the Suisse ADPKD cohort were collected from april 2006 to april 2011 and clinical and laboratory parameters as well as renal volumetry were assessed in 625 study visits. Urinalysis for routine parameters was performed on spot urine and 24-hour urine. A cox regression analysis was applied to model the effect of CKD stages and height-adjusted total kidney volumes and category on microhematuria.

Results: In a total of 98'848 patient-days (3268 patient-months), 45 events (7.2%) were observed in 28 patients (16%). The regression analysis of CKD stages at baseline revealed a ~2.9fold risk for developing microhematuria for patients with CKD stage 2 when compared to CKD stage 1. For CKD stage 3, the hazard ratio increased to ~3.5fold when compared to CKD 1. No events were recorded for CKD 0. A model for hTKV demonstrated a 6.5% risk increase per 100 cm³ additional volume of renal mass. The risk for patients to develop microhematuria in hTKV category 1 increased ~3.2 fold when compared to category 0.

Conclusions: The occurrence of Microhematuria in ADPKD is associated with increased kidney volume and advanced CKD stages.

Hyponatremia, hypokalemia, hypochloremia or metabolic alkalosis in cystic fibrosis: systematic review of the literature

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Background: Dyselectrolytemias (Na ≤ 134 mmol/L, K ≤ 3.4 mmol/L, Cl ≤ 100 mmol/L, HCO₃ ≥ 27 mmol/L) can be found in cystic fibrosis patients on drug treatment (especially diuretics and alkalizing agents). Hyponatremia and hypokalemia can also be found in cystic fibrosis patients with diabetes mellitus, a major comorbidity of this disease. Finally, cystic fibrosis sometimes per se tends to these dyselectrolytemias. The latter tendency, first documented >90 years ago, has never been addressed analytically. We therefore reviewed all the available literature.

Methods: We conducted a review of the literature using the principles underlying the UK Economic and Social Research Council guidance on the conduct of narrative synthesis and the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.

Results: The reports included 172 subacute and 90 chronic cases with a ratio of 1.6. Dyselectrolytemias were mostly associated with often clinically unapparent fluid volume depletion, mainly affected patients ≤5.5 years of age, frequently tended to recur and often were diagnosed before cystic fibrosis. Subacute presentation often included history of heat exposure, vomiting, excessive sweating and chest infection. History of chronic presentation, instead, was mainly inconspicuous. The tendency to dyselectrolytemias was similar between subacute and chronic cases, with hyponatremia being more pronounced (P <0.02) in subacute rather than in chronic presentation. Subacute cases were regularly managed, chronic ones instead were managed with oral salt supplementation.

Conclusions: We wish to warn physicians to be aware of the fact that these dyselectrolytemias can occur both as a presenting and as a recurring feature of cystic fibrosis.
Severe signs of dilutional hyponatremia secondary to desmopressin treatment for nocturnal enuresis: A systematic review of the literature

B. Lucchini, G.D. Simonetti, A. Ceschi, S.A.G. Lava, M.G. Bianchetti

Objective: Dilutional hyponatremia is a potentially serious adverse effect of desmopressin, a vasopressin analog that is widely prescribed to manage nocturnal enuresis. The presentation of hyponatremia, largely related to cerebral dysfunction, can include severe signs like altered mental status and seizures.

Methods: We reviewed all the available literature dealing with altered mental status or seizures in enuretic subjects on desmopressin. For this purpose we used the principles underlying the UK Economic and Social Research Council guidance on the conduct of narrative synthesis and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The retained publications included patients, who were described individually, revealing data on mode of administration, further identifiable factors predisposing to hyponatremia, presentation and clinical course.

Results: We found 31 reports containing a total of 54 (34; 20) cases (9.0 [6.5–11] years of age; median and interquartile range) of hyponatremia secondary to desmopressin treatment presenting with altered mental status (N = 8) or seizures (N = 46). In most cases the complication developed ≤14 days after starting desmopressin. An intranasal formulation had been used in 47 patients. Excess fluid intake was documented as a contributing factor in at least 22 cases. In 6 cases severe signs of hyponatremia developed in the context of intercurrent illnesses.

Conclusion: Altered mental status or seizures are very rare but recognizes the need for desmopressin in nocturnal enuresis. This complication mostly develops in subjects managed with the intranasal formulation ≤14 days after starting the medication, following excess fluid intake and during intercurrent illnesses.

Metabolic disturbances and renal stone promotion on treatment with topiramate: a systematic review of the literature

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Background: Topiramate, a drug prescribed for the management of epilepsy, for migraine headache prophylaxis and as a weight-loss agent, has been associated with the development of metabolic acidosis, hypokalemia, hyperuricemia and renal stone disease. Since textbooks do not mention this tendency, we systematically reviewed all the literature.

Methods: We used the principles underlying the UK Economic and Social Research Council guidance on the conduct of narrative synthesis and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Results: Forty-seven reports published between 1996 and 2013 were retained for the final analysis. Five case-control studies and 6 longitudinal studies addressed the effect of topiramate on acid-base and potassium balance. A significant tendency towards a mild to moderate hyperchloremic metabolic acidosis (with bicarbonate ≤21.0 mmol/L in approximately every third case) and mild hypokalemia (with potassium ≤3.5 mmol/L in 10% of the cases) was noted on treatment with topiramate, which was similar in children and adults. The use of topiramate was associated with a mild tendency towards hyperuricemia that was significant exclusively in male adults.

A tendency towards hypocitraturia, a recognized promoter of renal stone formation, was noted in all patients on topiramate.

Conclusions: Increasing evidence supports the use of topiramate. Topiramate is generally well tolerated and serious adverse events are rare. Nonetheless, the current systematic review of the literature indicates that its use is linked with the development of acidosis, hypokalemia, hyperuricemia and hypocitraturia.

Contrast-enhanced Ultrasound in the Diagnosis of Acute Pyelonephritis – an Interim-Analysis

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Introduction: Contrast-enhanced ultrasound (CEUS) has been described as a promising method for detecting acute pyelonephritis and its complications. Its sensitivity and specificity has been claimed to approach that of contrast CT, but the available data are very limited.

Methods: The “Triple P in UTI” study is a RCT that compares 2 different strategies regarding initiation and duration of antibiotic therapy and 2 algorithms for triage decisions in patients with UTI. In a substudy, all hospitalized patients with fever and/or flank pain undergo gray-scale, Doppler and contrast enhanced ultrasound (US) of both kidneys within 72h of admission. We report interim results of this substudy.

Results: 59 of 114 study patients were eligible for the substudy. 33 patients (56%) underwent study ultrasound, 8 (14%) refused to participate, and 18 (31%) missed the examination for various reasons. 3 of 33 patients (9%) showed signs of pyelonephritis by gray-scale and Doppler US, 2 patients (6%) exhibited underperfused areas that were only visible by CEUS. 28 patients (85%) showed no signs of pyelonephritis whatsoever. All findings were only recorded in the 24 patients with fever. In the 8 patients with fever and flank pain 3/8 studies were suggestive of pyelonephritis.

Conclusion: The present preliminary data suggest that early US has a low yield for signs of pyelonephritis in patients hospitalized for UTI with fever and/or flank pain. Findings are entirely restricted to patients with fever. In contrast, a substantial proportion will have abnormal US findings, if only patients with fever and flank pain are considered. CEUS appears to markedly increase the detection rate for pyelonephritic changes over that of gray-scale and Doppler ultrasound alone.
Serum calcification propensity predicts all-cause mortality in Chronic Kidney Disease stages 3 & 4

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Background: Arterial calcification is accelerated in patients with chronic kidney disease (CKD), and is strongly associated with arterial rigidity and cardiovascular mortality. We have recently developed a novel in vitro test which determines calcification propensity in patient blood. Here, we tested the hypothesis that increased serum calcification propensity is associated with progressive aortic stiffening and predicts all-cause mortality in CKD 3 & 4 and may prove a useful guide for the screening and therapeutic targeting of serum calcification propensity.

Methods: We determined the calcification propensity of serum samples from a historic cohort of CKD 3 & 4 patients (n = 184) with 5 years follow-up and correlated these values with aortic stiffening, survival, and known determinants of calcification propensity.

Results: Major determinants of serum calcification propensity included higher serum phosphate, ionized calcium, increased bone osteocalcin (HbA1c), SUV and lower free fetuin-A, plasma phosphatase and albumin concentrations. Serum calcification propensity was independently associated with aortic pulse wave velocity and with progressive aortic stiffening. The risk of death among patients in the highest tertile (crude HR 4.9; 95% CI, 2.0 to 11.8, P = 0.01; adjusted HR 2.2; 95% CI, 1.1 to 5.4, P = 0.04). This effect was lost, after further adjustment for aortic stiffness, suggesting a shared causal pathway.

Conclusion: Our newly developed serum calcification propensity test predicts all-cause mortality in CKD 3 & 4 and may prove a useful guide for the screening and therapeutic targeting of serum calcification propensity.

Association of ambulatory blood pressure with 17α-hydroxylase activity in the general population

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Background: The CYP17A1 locus was associated with blood pressure in genome-wide association studies. CYP17A1 encodes for 17α-hydroxylase/17,20-lyase, an enzyme involved in steroid metabolism. We explored the distribution of this enzyme activity in 17α-hydroxylase/17,20-lyase (CYP17A1) activity in the general adult population, its heritability and association with blood pressure.

Methods: In the Swiss Kidney Project on Genes in Hypertension study, urinary excretion (separated for day and night) of steroid hormone metabolites (measured by gas chromatography-mass spectrometry) were assessed in 140 men and 400 women randomly selected from the general population. Activity was estimated indirectly by two ratios: ratio 1 = (tetrahydro-11-dehydrocorticoosterone + tetrahydrocorticoestrone + 5α-tetrahydrocorticosterone + 5α-tetrahydrocorticosterone + 5α-tetrahydrocortisol + 5α-tetrahydrocorticosterone) and ratio 2 = (tetrahydro-11-dehydrocorticoestrone + tetrahydrocorticoestrone + 5α-tetrahydrocortisol + 5α-tetrahydrocorticosterone + 5α-tetrahydrocorticosterone + 5α-tetrahydrocortisol) / (androsterone + etiocholanolone). Ambulatory blood pressure was measured using Diasys Integra devices. We used a mixed linear model to explore the association of ambulatory blood pressure with log-transformed CYP17A1 activity exploring effect modification by urinary sodium excretion.

Results: Day-night CYP17A1 heritabilities [SE] were 0.71 [0.09], 0.55 [0.09] for ratios 1 and 0.39 [0.10], 0.40 [0.09] for ratios 2. CYP17A1 ratio 2 was associated positively with day and night systolic and diastolic ambulatory blood pressure (P <0.05), including an effect modification by urinary sodium excretion (P interaction <0.05), whereas no such association was found for ratio 1.

Conclusions: Estimated CYP17A1 activity is heritable. Lower estimated CYP17A1 activity is associated with higher ambulatory blood pressure, in particular under high salt intake. Our results suggest a role of CYP17A1 activity in blood pressure control in the general population.

Local Aldosterone Production in Human Umbilical Vein Endothelial Cells (HVEUC)

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Introduction: Aldosterone is an important mediator of a healthy pregnancy outcome not just providing for enhanced plasma volume but also supporting placental growth and angiogenesis. Since fetal well-being is directly affected by aldosterone deficiency, not only maternal adrenal aldosterone production should be considered.

Hypothesis: We hypothesized that the fetus supports appropriate placentation function by local aldosterone production in endothelial cells within the fetal umbilical-placental circulation.

Aim: We aimed to identify local endothelial aldosterone production.

Methods: As initial readout, we incubated either HUEVECs or HVSMECs with aldosterone with or without the aldosterone antagonist spironolactone. PI GF, an important factor for placental angiogenesis, which is known to be induced by aldosterone in trophoblasts was not influenced by the addition of aldosterone. A small but consistent decrease in PI GF expression following treatment with spironolactone was observed, suggesting local aldosterone production. In HUEVECs, we identified large amounts of CYP11B2 (aldosterone synthase) protein and aldosterone production from progesterone, DOC and cortisone, nearly five times higher than aldosterone production was stimulated upon the addition of known agonist of aldosterone, angiotensin II and VEGF. Cultured trophoblasts (primary human first/third trimester, JEG-3, BeWo) though aldosterone responsive did not produce aldosterone themselves.

Conclusions: Maternal aldosterone production is strategically located close to the placenta to be controlled by fetal factors allowing appropriate aldosterone availability, a survival factor for the fetus. Further studies will have to provide the expression pattern within different vascular beds and factors stimulating local aldosterone production.

Another Unexpected Role of Aldosterone in Pregnancy: Placental Angiogenesis via PI GF Induction

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Angiogenic signals are vital for placental integrity beyond trophoblast proliferation, the later having been shown to be related to aldosterone by our group. As aldosterone has been shown to enhance placental growth factor (PI GF) expression in peripheral vessels via a functional mineralocorticoid receptor responsive element in its promoter region, we hypothesized that aldosterone adapts placental angiogenesis to trophoblast growth by secreting PI GF. We analysed TH-Aldosterone concentrations in urine (by GC-MS) and PI GF in the serum (by Elisa) of 34 pregnant women throughout pregnancy. We observed a direct linear correlation between TH- Aldosterone and PI GF. We excluded aldosterone secretion secondary to PI GF in the adrenal cell line H295R. Next, we incubated the human choriocarcinoma cell line BeWo and third trimester human primary trophoblast cells alone and in combination with known PKA inhibitor forskolin, increasing amounts of aldosterone (10−10 to 10−8 M) and the competitive aldosterone receptor blocker spironolactone for 6 and 24 hrs. PI GF mRNA was stimulated upon the addition of different aldosterone concentrations in primary human and also the trophoblast cell line BeWo in combination with forskolin, PI GF protein expression increased upon addition of aldosterone in human primary trophoblasts. Preliminary experiments in culture conditions with low glucose and addition of H-89, a PKA inhibitor, indicated stimulation of the system upon starvation via the PKA pathway. We conclude that aldosterone is a major stimulator of PI GF expression in pregnancy likely accounting for the majority of circulating PI GF. This adds a further novel protective mechanism for aldosterone in pregnancy, thus responding via this steroid hormone to unfavourable environmental conditions.
A successful pregnancy requires an accommodating environment. Salt and water availability are critical for plasma volume expansion. Any changes in sodium intake would alter aldosterone, a hormone previously described beneficial in pregnancy. We hypothesized that increased aldosterone is a rescue mechanism and appropriate salt availability is equally effective in maintaining a normotensive blood pressure. We compared normotensive pregnant women (n = 31) throughout 1 year of age – A retrospective matched-pair analysis. A retrospective matched-pair analysis

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Objective: Due to increased expectation of life, there is a growing number of older patients with end stage renal disease (ESRD) requiring renal replacement therapy (RRT). However, there is a lack of data with regard to clinical outcomes as well as the economic impact of these patients on our health care system.

Methods: In this single centre study, we retrospectively analyzed two groups of patients on chronic hemodialysis stratified by age. A group of patients above 70 years of age ("seniors"); n = 69) was compared with a matched control group of patients between 60 and 69 years of age ("elderly"); n = 39). The main investigated outcomes were patient survival, causes of death and frequency of complications.

Results: There was only a trend towards a better survival in elderly regarding Kaplan Meier curves (p = 0.06). During the observational time, about half of the patients died, i.e. 38/69 in the senior and 14/39 in the elderly group, respectively (p = 0.07) and cause of death was mostly unknown. Both groups were affected equally by complications during hemodialysis therapy (p = 0.62). Comparing the severity of complications, the only significant difference was triggered by a higher frequency of outpatient treatment in seniors (p = 0.04). However, there were not more severe complications in seniors leading to hospitalization (p = 0.64).

Conclusion: Age is not a good predictor for the outcome of patients above 70 years with ESRD requiring RRT. Thus, further investigations are needed, taking the growth of this patient group into account.

Comparison of two different cholecalciferol supplements (multivitamin tablets versus oil-based droplets) in patients on long-term hemodialysis (HD)

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Background: Many types of vitamin supplements exist on the market but no data are available comparing in HD patients the effects of different cholecalciferol (VitD3) preparations. The aim of this study was to compare the long-term results of VitD3 supplementation with either multivitamin tablets (MT) or oil-based droplets (OD).

Patients and methods: Since a few years all the patients of our center having low baseline 25(OH)D levels, receive a sytematic VitD3 supplementation either on a post-dialysis basis with MT (Dialvit, D. Bichsel AG, Intertaken, 2000 IU/dial) or on a weekly basis with OD (Oleovit D3, Fresenius Kabi, 400 IU/droplet) to maintain the 25(OH)D levels in an optimal range of 75–150 nmol/l. The choice of the mode of supplementation was based on patients' preference. At the moment of this evaluation all the patients had received a regular supplement of VitD3 for a minimum of one year. Thirty-five patients (mean ± SD age 69.9 ± 9.5 years, 19 males) were evaluated, receiving either MT (n = 20) or OD (n = 15).

Results: The 25(OH)D concentrations were similar in the two groups both before (29.5 ± 35.7 ± 17.3 nmol/l, p = NS) and under VitD3 supplementation (107.1 ± 17.4 vs 113.6 ± 29.6 nmol/l, p = NS). The parameters of the bone-mineral metabolism – i.e. pre-dialysis total/ionizated calcium, phosphate, alkaline phosphatase, i-PTH and calcitriol – did not significantly differ between the 2 groups. However to obtain similar 25(OH)D blood levels the mean dose of cholecalciferol prescribed was more than the double in the OD group compared to the MT one (14800 ± 5943 IU/week vs 7100 ± 3339 IU/week, p <0.001).

Conclusions: These results shows that to obtain similar blood levels of 25(OH)D a much higher dose of cholecalciferol should be prescribed when using oil-based supplements compared to multivitamin tablets.
Large variations in pulse wave velocity and reflection patterns occur during a hemodialysis session and are not related to the degree of ultrafiltration.

**Methods:** A total of 13 hemodialysis patients undergoing ultrafiltration (UF) and 8 patients dialyzed at stable body weight (SW) underwent applanation tonometry using the Compilor and the Sphygmocor devices to measure carotid-to-femoral pulse wave velocity (PWV) and the central systolic augmentation index (Aix), respectively. Measurements were taken just before, halfway through, and just after a standardized hemodialysis session (duration: 4 hours; dialysate concentrations: calcium 1.25 mEq/L, potassium 2 mEq/L, bicarbonate 28 mEq/L, temperature 36 °C). **Results:** There was a similar decrease in Aix, central and peripheral BP in both the UF- and the SW-group. There was a statistically significant (p<0.001) but physiologically minor increase in PWV throughout the dialysis session in both the UF (from 10.9 ± 3.5 to 11.5 ± 3.0 m/sec) and SW (from 10.4 ± 2.1 to 11.0 ± 2.4 m/sec ) groups (ΔPWVrend = 0.97), with large individual fluctuations occurring in each group (see figure). **Conclusion:** Independently of ultrafiltration, important changes in arterial wall properties occur during hemodialysis, which may account for the heterogeneous hemodynamic responses observed during dialytic sessions.

Assessment of subjective and hemodynamic tolerance of different high- and low-flux dialysis membranes in patients undergoing chronic intermittent hemodialysis: a randomized controlled trial

**Background:** High- and low-flux dialysis membranes can induce different intradialytic hemodynamic profiles. This study aimed to compare hemodynamically some of the commonly used polysulfone dialyzers in Switzerland.

**Methods:** We performed an open label, randomized, cross-over trial, including 25 hemodialysis patients. Four 1.8 m² polysulfone dialyzers, A (Revaclear, Gambro), B (Helixone high-flux, Fresenius), C (Xevonta, BBraun) and D (Helixone low-flux, Fresenius), were compared with each other. The hemodynamic profile was assessed with a non-invasive technique and patients were asked to provide tolerance feedback.

**Results:** The mean score (± SD) subjectively assigned to dialysis quality on a 1-10 scale was: A 8.4 ± 1.3, B 8.6 ± 1.3, C 8.5 ± 1.6, D 8.5 ± 1.5. KBV was: A 1.58 ± 0.30, B 1.67 ± 0.33, C 1.62 ± 0.32, D 1.45 ± 0.31. The low-compared to the high-flux membranes, correlated with higher systolic (128.1 ± 13.1 vs. 125.6 ± 12.1 mm Hg, P <0.01) and diastolic (76.8 ± 8.7 vs. 75.3 ± 9.0 mm Hg; P <0.05) pressures, higher peripheral resistance (1.44 ± 0.19 vs. 1.40 ± 0.18 *mmHg/ml/min; P <0.05) and lower cardiac output (3.76 ± 0.62 vs. 3.82 ± 0.59 l/min; P <0.05). Hypotension events (decrease in systolic blood pressure by >20 mm Hg) were 70 with A, 87 with B, 73 with C and 75 with D (P <0.01 B vs. A, 0.05 B vs. C and 0.07 B vs. D).

**Conclusions:** The low-flux membrane correlated with higher blood pressure levels compared to the high-flux ones. The Helixone high-flux membrane ensured the best efficiency. Unfortunately, the very same dialyzer correlated with a higher incidence of hypotensive episodes, eventually due to an efficiency-mediated imbalance. Despite these findings, subjective tolerance to the various filters was comparable.

Cinacalcet based management of secondary hyperparathyroidism in Swiss hemodialysis patients: 12 months data of the TRANSIT observational study

**Background:** Arteries of end-stage renal disease patients are characterized by accelerated atherosclerosis and chronically progressive arterial stiffening. The acute effects 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:** We performed an open label, randomized, cross-over trial, comparing hemodynamically some of the commonly used polysulfone different intradialytic hemodynamic profiles. This study aimed to compare hemodynamically some of the commonly used polysulfone dialyzers, A (Revaclear, Gambro), B (Helixone high-flux, Fresenius), C (Xevonta, BBraun) and D (Helixone low-flux, Fresenius), were compared with each other. The hemodynamic profile was assessed with a non-invasive technique and patients were asked to provide tolerance feedback.

**Results:** The mean score (± SD) subjectively assigned to dialysis quality on a 1-10 scale was: A 8.4 ± 1.3, B 8.6 ± 1.3, C 8.5 ± 1.6, D 8.5 ± 1.5. KBV was: A 1.58 ± 0.30, B 1.67 ± 0.33, C 1.62 ± 0.32, D 1.45 ± 0.31. The low-compared to the high-flux membranes, correlated with higher systolic (128.1 ± 13.1 vs. 125.6 ± 12.1 mm Hg, P <0.01) and diastolic (76.8 ± 8.7 vs. 75.3 ± 9.0 mm Hg; P <0.05) pressures, higher peripheral resistance (1.44 ± 0.19 vs. 1.40 ± 0.18 *mmHg/ml/min; P <0.05) and lower cardiac output (3.76 ± 0.62 vs. 3.82 ± 0.59 l/min; P <0.05). Hypotension events (decrease in systolic blood pressure by >20 mm Hg) were 70 with A, 87 with B, 73 with C and 75 with D (P <0.01 B vs. A, 0.05 B vs. C and 0.07 B vs. D).

**Conclusions:** The low-flux membrane correlated with higher blood pressure levels compared to the high-flux ones. The Helixone high-flux membrane ensured the best efficiency. Unfortunately, the very same dialyzer correlated with a higher incidence of hypotensive episodes, eventually due to an efficiency-mediated imbalance. Despite these findings, subjective tolerance to the various filters was comparable.
Effect of PA21, a New Iron-Based Phosphate Binder on FGF23 and Vascular Calcifications in Uremic Rats

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Elevated serum phosphate and FGF23 levels are associated with cardiovascular disease in patients with chronic renal disease. Whether FGF23 can act on vascular calcification is still on debate. Few studies have analysed how to suppress FGF23 up-regulation using phosphate binders. The aim of this study was to evaluate the effects of PA21 compared with lanthanum carbonate (La) and sevelamer carbonate (Se) on serum FGF23, phosphorus, calcium, iPTH concentrations and to investigate a potential effect on the development of vascular calcifications in an adenine-induced rat model of CRF. After induction of CRF through a 4 week adenine-diet, renal function was significantly impaired in all groups. All uremic rats developed severe hyperphosphatemia and serum PTH increased significantly. The concentration of each binder was adjusted in all groups to reach similar serum phosphate levels. The concentration of each binder was then: PA21 2% (1% iron), La 2% (1% lanthanum), Se 1.5% (1% sevelamer). A computer-assisted automated quantitative von Kossa stained vessel sections. Amorphous primary and crystalline secondary CPP were identified by TEM. Supplementation of DMEM/10% FBS with 3.5 mM phosphate led to a time-and temperature-dependent generation of primary and secondary CPP. Exposure of VSMC to CPP led to a pronounced accumulation of calcium and phosphate content of cells and Alizarin red staining. Sulforhodamine B was used to estimate cell viability. STS-culture and co-culture experiments were performed with VSMC and HepG2 cells. Results: Both amorphous primary CPP and crystalline secondary CPP could be identified by TEM. Supplementation of DMEM/10% FBS with 3.5 mM phosphate led to a time- and temperature-dependent generation of primary and secondary CPP. Exposer of VSMC to CPP led to a pronounced accumulation of calcium and phosphate/calcification within 7 days. Exposure of cotransfecting VSMC to STS led to an augmentation of calcification, whereas H2S (used as a control) inhibited calcification. In contrast, STS prevented calcification when VSMC were grown in co-culture with hepatocyte cell line HepG2. Further analyses showed a consumption/metabolization of STS by HepG2, but not by VSMC. Conclusion: CPP induce calcification in this in vitro model of VSMC, and STS prevents the calcification provided that hepatocytes are present. It is tempting to speculate that the calcification-preventing effect of STS might be mediated by H2S, produced by STS-exposed liver cells.

Phosphate binders were then given for 4 weeks to all uremic rats, except for the uremic control rats. The concentration of each binder (% of binder added to the diet) was chosen to deliver approximately the same amount of active pharmaceutical moiety to each rat: PA21 5% (corresponding to 1% iron), La 2% (1% lanthanum), Se 1.5% (1% sevelamer). A computer-assisted automated quantitative measurement was used to assess the degree of calcification from von Kossa stained vessel sections. Hyperphosphatemia and increased serum PTH levels were controlled in the phosphate binder treated groups to the same extent. PA21 was the only phosphate binder that was associated with a decrease of FGF23. In uremic control rats, vascular calcifications were more prominently present in the thoracic aorta compared to the carotids and the abdominal aorta. Vascular calcifications of thoracic aorta were significantly decreased by the three phosphate binders to a similar extent. PA21 was more efficient than lanthanum carbonate to prevent calcifications in the upper part of the thoracic aorta. PA21 was as effective in the control of hyperphosphatemia, secondary hyperparathyroidism and vascular calcifications as La and Se. The role of FGF23 as a potential factor of calcification needs to be further evaluated.

Summary: TRANSIT confirms in a real-life setting, that shPT treatment with cinacalcet helps to reach iPTH and P/t targets. The impact of Cinacalcet initiation on calcium target achievement remains to be further evaluated.
Sodium thiosulfate prevents the formation of mineral matrix vesicles in uremic rats
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Background: Chronic kidney disease (CKD) is associated with vascular calcification and this is the main cause of death in these patients. The adenine rat model develops CKD along with vascular calcification. Sodium thiosulfate (STS) prevents vascular calcification in this model, but mechanism has not been elucidated yet. Our hypothesis is that STS prevents calcification via its anti-oxidative properties.

Methods: Male wistar rats (n = 50, 8-weeks old, 5 groups) were fed an adenine (Ad) diet for 4 weeks followed by a phosphate diet for 6 weeks. NaCl (NNaCl and AdNaCl group) or STS (Ad STS group) were injected i.p. 6 times per week for 6 weeks. The antioxidants apocynin (AdAPO group) or taurin (AdTAU group) were added to the drinking water and food, respectively. Kidney function was determined at week 0, 4 and 10. Histology, tissue calcium and TEM ultra-structural analyses were performed after sacrificing the animals at week 10.

Results: Renal function declined in all Ad-treated animals. Medial aortic calcification and calcium content were vastly decreased in STS-treated animals when compared to untreated uremic controls, as well as APO- and TAU-treated animals. Like in the aorta, calcium content in heart and kidney tissue was significantly decreased in the AdSTS group. TEM of aortic tissue showed the abundance of calcium- and phosphate-containing matrix vesicles in AdNaCl, AdAPO and AdTAU groups but not in the AdSTS group.

Conclusion: STS prevents vascular calcifications by preventing medial matrix vesicle formation. This finding was not observed in animals treated with the anti-oxidants APO or TAU, but was unique to STS.

Modern MicroCT: analysis of whole mouse kidney down to capillary level

Background: Nephron number and glomerular volume are the key characteristics of the morphological substrate of the renal function. The accurate estimation of these parameters has become increasingly important because their alterations may play a significant pathophysiological role in the development or progression of a range of nephropathies and various “kidney-related” pathologies.

Present situation: The gold-standard method of the kidney morphometry at the moment is the exhaustive physical fractionator/ dissector method (often combined with Cavalieri for kidney volume estimation). Although accepted as standard, it is extremely time-consuming and laborious.

Aim: to develop a technique that would allow fast and reliable estimation of such parameters as nephron number, glomerular volume, glomerular size distribution and kidney volume.

Results: using the modern high-resolution microCT (SkyScan-1172) and novel Angiofil contrasting medium we managed to visualize the whole mouse kidney vasculature in 3D with the spatial resolution of approx. 2 µm. Based on the obtained datasets, the mentioned parameters can be obtained already within 24 hours after the harvesting of the kidney. Moreover, after the microCT-scan it is possible to process the same kidney for the histological analysis of the site of interest.

Conclusions: the developed technique allows fast (~24 hours) and reliable kidney morphometry based on high-resolution microCT-scans of the kidney vasculature in 3D. Besides classical kidney morphometry, it provides the data on the vasculature which makes the technique even more beneficial for pathological processes with involvement of the vasculature. Possibility of further histological analysis is another major advantage of the technique.

TREX1 mutations – one of the genetic causes for renal vascular diseases in younger Patients
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In most cases, vascular pathology in renal biopsies is due to hypertension, diabetes mellitus or more rarely inflammatory processes. Infrequently, it manifests as thrombotic microangiopathy. In addition to immuno-mediated pathomechanisms like in hemolytic uremic syndrome and disseminated intravascular coagulation, toxemia of pregnancy and drug-induced causes, there are also genetically defined illnesses causing thrombotic microangiopathy.

We present two Caucasian male patients (aged 37 and 30 years at first presentation) who had suffered from migraine-like headaches for years and experienced neurologic complications and progressing failure of other organ systems. A renal biopsy was performed due to chronic renal failure in both patients. It demonstrated severe stenosing arteriolythiasis, internal fibrosis of interlobular arteries and glomerular abnormalities showing irregular basement membranes. The findings were considered to be due to thrombotic microangiopathy.

Several years after having performed the renal biopsies, the symptoms of the patient could be attributed to hereditary systemic angiopathy (HSA), as a mutation in the TREX1-gene was found. HSA is part of the family of syndromes linked to alterations on chromosome 3p21.3. The role of this gene in the pathogenesis of the disease in our patients was corroborated by the recently published genome-wide association studies. The 33kDa mediator of ErbB2 induced cell motility (Meme) protein interacts with fibroblast growth factor (FGF), insulin receptor substrate protein 1, and estrogen signaling, but its physiological role is still poorly understood. Inductive Meme knockout 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 hypercalcemia, elevated 1,25-OH D3 and suppressed PTH. We hypothesize that Meme is expressed in the bone and required for the bone’s FGF receptor signaling and the regulation of FGF-23 secretion.

Tissues of C57BL/6 mice were prepared for qPCR (male, age 2 to 8 weeks) and immunoblotting (both sexes, aged 66 to 180 days) using specific probes and anti-Meme antibodies respectively. Meme has been detected by Western blot in tibia, cortical femur, femur bone marrow, kidney, muscle, skin, heart, lung, liver, spleen, thyroid gland, testis, all intestinal segments, and bladder. Meme protein expression was higher in bone fractions than in the kidney (3 independent experiments) and other organs. Over time, Meme mRNA levels in tibia of male mice increased between week 2 to 4, then decreased at 6 weeks reaching lowest levels at 8 weeks of age. Meme is expressed widely, such as in the main sites of calcium and phosphate regulation, the bone, intestine and kidney. The peak of bone Meme mRNA at 4 weeks, which correlates with maximal growth in mice suggests that Meme could be involved in developmental processes such as longitudinal growth. The next steps will be in vivo (micro-CT, bone RNA microarray, serum analyses) and in vitro (bone cell staining and functional assays) experiments in an inducible whole-body Meme KO mouse model.

Vascular pathology in renal biopsies based on distinct genomic alterations should be kept in mind by nephropathologists, especially in younger patients and might have major impacts on the further treatment of the patients.
Fibrosis of Solid Organs: Towards a Common Classifier across Species
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Background: We described a transcriptomic classifier of metazoan and related genes (MARGS) discriminating renal allograft biopsies without fibrosis and extended analyses to non-transplant solid organs (AJT,2009; Virochows Arch,2011). We now apply our MARGS-based algorithm to a rat model of age-induced interstitial renal fibrosis.

Methods: Untreated Fischer 344 rats (n = 78) were sacrificed at 2 to 104 weeks of age. For gene expression studies we used single color (Cy3) Agilent Whole Rat Genome 4x44k microarrays; males: n = 4 at weeks 2, 5, 6, and 8; n = 5 at weeks 15, 21, 78, and 104; females: n = 5 at weeks 2, 5, 6, 8, 15, 21, 78 and 104. Intensity data were subjected to variance stabilization including log2 transformation (www Partek.com). Data were analyzed with ANOVA using gender/age as factors and with Pearson correlation.

Results: Fibrosis severity increased with age. Across age groups 60 MARGS were differentially expressed. PCA visualized segregation of age groups by gender from week 6. More MARGS were differentially expressed in older males than in older females. Expression levels of MMP-7 correlated best with fibrosis grade. Expression values of 15/19 genes of the original classifier present on Agilent array, in conjunction with linear discriminant analysis, were able to classify samples with fibrosis in aging.

Conclusions: Our MARGS classifier represents a cross-organ and cross-species classifier of fibrosis irrespective of etiology. This finding provides evidence for a common pathway leading to fibrosis.

The Spectrum of Renal Pathology Findings in Armenian and Swiss Children: Differences and Similarities – Comparison of two Decades
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Background: Renal biopsy findings vary considerably, not only between different countries, but also with time. Based on similar biopsy policy and joint work-up we compared biopsy data of native kidneys of children in Armenia and Switzerland obtained during the last two decades.

Methods: A total of 487 renal biopsies performed during 1993–2002 and 2003–2012 were analyzed; 253 were from Yerevan (EYN; age 0.8–18 years (11.2 ± 4.6); 56% males) and 234 from Zurich (ZRH; age 0.1–18 years (8.7 ± 4.8); 61% males). Evaluation was done by light microscopy (LM) in EYN and – after exclusion of amyloidosis – in ZRH by LM, electron microscopy (EM) and immunohistochemistry (last 79).

Results: The most striking difference concerns the high frequency of amyloidosis secondary to Familial Mediterranean Fever (FMF) in Armenia (25.4% in the first and 19.4% in the second decade vs. 0% in ZRH). In contrast, IgA-nephropathy (IgAN; both isolated and associated with Henoch Schönlein purpura) was seen considerably more often in Switzerland (27.8%) than in EYN (8.3%). Whereas IgAN in ZRH slightly declined from 30.2% to 26.1% (1st vs. 2nd decade), it increased in Armenia from 6.1% to 10.1%. – Certain forms of glomerulonephritis (membranoproliferative type I and membranous) and primary focal segmental glomerulosclerosis tended to be more frequent in Armenia than in Switzerland.

Conclusions: The study allows a direct comparison between renal biopsy findings of two countries and two different time periods. The large number of amyloid nephropathy due to Familial Mediterranean Fever in Armenia is alarming despite a decline in the second decade. In contrast, IgA-nephropathy was more prevalent in Switzerland.

Uninephrectomy of HFD-induced obese mice greatly accelerates proteinuria, fibrosis and changes in gene expression
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Obesity has been reported as an independent risk factor for chronic kidney disease which causes glomerulosclerosis and renal insufficiency. To assess the relationship between a reduced nephron number and a particular susceptibility to obesity-related renal damage, mice underwent uninephrectomy (UNX) followed by either normal or high-fat diet (HFD) and were compared with sham operated control mice. After 20 weeks of diet intervention, hyperlipidemic control mice presented characteristic features of progressive nephropathy: albuminuria, renal fibrosis and overexpression of transforming growth factor (TGF)-β1-Smad. These changes were even higher in hyperlipidemic mice underwent uninephrectomy. Moreover, evaluation of gene expression in the kidneys by whole mouse genome microarrays indicate that gene families involved in cytoskeleton remodeling, fibrosis and lipid metabolism were more up-regulated in the UNX-HFD group. Interestingly, the microarray analysis and with histological investigation are suggestive of possible roles of Fxr in this model of renal damage. The results shed a light on unravelling complex mechanisms contributing to high-fat diet induced renal damage.

Coupling between transcellular Na+ transport and paracellular permeability in collecting duct cells
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The aldosterone-sensitive distal nephron is responsible for the fine-tuning of Na+ balance. According to dietary Na+ intake and aldosterone levels, collecting ducts (CD) are subjected to large variations of Na+ transport. In CD, Na+ reabsorption occurs mostly through principal cells via a transepithelial pathway that sequentially involves apical Na+ channels (ENaC) and basolateral Na,K-ATPase. Several strands of interconnected tight junctions prevent paracellular ion permeability and especially Na+ back flux. We hypothesized that, independently of hormonal stimulus, transcellular Na+ fluxes cross talk with tight-junctions in order to prevent back flux of reabsorbed Na+. Overexpression of γ-ENaC that increases transcellular Na+ flux in cultured mouse collecting duct cells enhanced transepithelial resistance. Time-course experiments revealed that current increased first followed by increased transepithelial resistance. Overexpression of γ-ENaC increased total and Triton X-100 insoluble γ-ENaC. Interestingly, γ-ENaC protein abundance. However, only claudin-8 mRNA levels were increased in response to γ-ENaC indicating that a primary increase in claudin-8 protein level may secondarily stabilize claudin-4 and increase its abundance. The increase in Triton X-100 insoluble claudin-4 and 8 abundance was associated with increased Triton X-100 insoluble E-cadherin and β-catenin protein abundance.

Our results reveal a coupling mechanism between transcellular Na+ transport and paracellular permeability. This coupling involves the selective regulation of both tight-junction and adherens junction components. We are currently assessing the cellular mechanism of the observed increase in claudin-8 expression as well as the signaling pathways involved in this rearrangement of intercellular junctional complexes.
Furosemide stimulation of parathyroid hormone in humans: role of the calcium-sensing receptor and renin-angiotensin system. Valentina Form Ogna, Marie-Eve Muller, Marc Mailard, Carole Zwieacker, Grégoire Wuerzner, Olivier Bonny, Michel Burniere

Introduction: Experimental and clinical studies have reported that furosemide administration increases plasma parathyroid hormone (PTH), but the mechanism remains unknown. Experiments on rats suggested that calcimimetics could blunt this effect. We aimed to investigate the role of the calcium sensing receptors (CaSR) in mediating the acute effect of furosemide on PTH in humans. We explored interactions between cinacalcet, PTH, renin (PRA) and aldosterone secretion in response to furosemide.

Methods: This randomized placebo-controlled cross-over study included 18 males subjects, randomly assigned to receive either a dose of 60 mg cinacalcet orally or placebo. Furosemide 20 mg was injected in 13 subjects after 3 hours. Intact PTH, PRA, aldosterone, plasma and urinary electrolytes were measured at baseline, before furosemide injection and regularly thereafter.

Results: Oral cinacalcet suppressed plasma PTH (p = 0.002). Furosemide produced a rapid sharp increase in PTH in subjects under placebo (p = 0.001). In subjects pre-exposed to cinacalcet, the PTH response was significantly blunted, whereas no PTH change was observed in furosemide-naïve subjects. No significant changes were recorded in plasma electrolytes. PRA and aldosterone were stimulated by furosemide injection, and not altered by previous cinacalcet exposition.

Conclusion: In conclusion, our results indicate that furosemide acutely stimulates PTH secretion, in absence of any electrolyte changes in humans. The CaSR is mediating a significant part of this effect. These observations emphasize the role of the CaSR at the interface between both calcium and sodium regulatory systems.

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Impact of uninephrectomy on body L-arginine homeostasis and blood pressure control in mice Samyuktha M. Pillai and François Verrey. Institute of Physiology, University of Zurich

L-arginine plays an important role, acting as a precursor for a variety of physiologically important substances including citrulline, urea, ornithine, proline and nitric oxide. Due to the role that L-arginine plays in NO synthesis, it acts as a limiting factor for the amount of NO present. The aim of this study is to test the hypothesis that UNX impacts on the metabolism of L-arginine and its metabolite asymmetric dimethylarginine (ADMA) and thereby also on endothelial NO production and 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. The concentrations of plasma amino acids and other parameters were analyzed. Telemetry measurements were also performed to compare and verify the blood pressure changes from tail cuff. We observed an increase in size of the remnant kidney post UNX. Measurements were conducted using tail cuff and the blood pressure was observed to be higher in UNX mice post-surgery and also higher compared to sham operated ones post-surgery. This difference is maintained from day 10 to day 30 after surgery. To confirm these differences, telemetry measurements were conducted and the UNX mice were observed to show an elevated mean arterial pressure and systolic pressure. Telemetry measurements to confirm BP changes with the same animal before and after surgery are currently underway. The impact of uninephrectomy in relation to eNOS and blood pressure control is of particular interest since in situations such as kidney failure there is an increase in blood pressure which has been shown to be associated with changes in L-arginine, ADMA and NO levels. Measurements of the levels of arginine and its methylated forms were conducted and plasma concentration of ADMA was found to be higher in the UNX animals. Another aspect of this project is to check the impact of uninephrectomy on mice that lack arginase II and whether this deficiency can compensate for the reduced arginine production that is expected as a consequence of uninephrectomy. Additionally, it is currently being tested whether citrulline supplementation may compensate for a potential change in L-arginine post-surgery.
Comprehensive Analysis of Hypoxia-Regulated Gene Transcripts in Chronic Kidney Disease and Renal Cells

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Most chronic kidney diseases (CKD) are initiated as glomerular damage with loss of glomerular capillaries. The best morphologic indicator of disease progression and development of end-stage renal disease, however, is interstitial fibrosis accompanied by capillary rarefaction. As hypoxia has been associated with fibrosis the question arises whether renal cells indeed face hypoxia in CKD and respond with a transcriptional program which could lead to progression of renal disease.

Expression of hypoxia-associated genes in genome-wide expression profiles of more than 160 renal biopsies from patients with different CKD stages revealed correlation of HIF-target genes with eGFR in the cortical tubulointerstitium and glomerular samples. These correlations were both positive and negative and in part compartment-specific. To study the cell-type-specific response to hypoxia and the relevance of given HIFs we investigated gene expression profile of HK-2 cells and podocytes with stable HIF-1α and/or HIF-2α suppression under hypoxic conditions. In HK-2 cells microarray analysis revealed 163 (86% HIF-1α and/or HIF-2α dependent) significantly up- and 31 (81%) downregulated hypoxia target genes. In podocytes, 416 (47% HIF-1α and/or HIF-2α dependent) genes were significantly up- and 318 (85%) downregulated. To validate the results on protein level immunohistochemistry of HIF-target genes in human biopsies with different GFRs was established and showed a similar pattern to correlation analysis. Our gene expression studies do not indicate an over-all hypoxic milieu in acquired kidney diseases. However, the data clearly point to compartment- and cell-type-specific dysregulation of hypoxia-associated gene transcripts.

Poster presentations – NCCR Kidney.CH

Proteomic Study of FFPE IgA Nephropathy Biopsy Tissue by Using OSSD and SWATH-MS Methods

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IgA nephropathy (IgAN) is the most common cause of primary glomerulonephritides in developed countries. Up to 50 percent of these patients undergoing progressive disease ultimately leading to end-stage renal disease. Current prognostic scores, which rely on histology and clinical characteristics, have limited accuracy to predict disease course and allied treatment decisions. To achieve a better understanding of IgAN, an efficient high-throughput workflow for the proteomic analysis of IgAN biopsy tissues, especially their glomerular compartment was established by combining two new techniques: On-site Direct Digestion (OSDD) and SWATH mass spectrometry (SWATH-MS).

Using formalin-fixed paraffin-embedded (FFPE) IgAN biopsy specimens (n = 10), at least 50 glomeruli (estimated tissue area 1 mm²) were collected by laser microdissection (LMD) from tissue sections with 10 µm thickness. Peptides were extracted from the pretreated glomerular sections using OSSD – a new proteomic sample preparation protocol – then purified by C18 StageTip™. A data independent MS acquisition method (SWATH-MS) was used to survey all peptide ions and their fragment ions. A targeted data analysis strategy using the software tool OpenSWATH was used to analyze the SWATH-MS data sets.

Using this integrated new strategy, we identified and quantified more than 2400 proteins with very high stringency (FDR <1%) in each sample. Comparing normal glomerular data, C7, C3, IgA and other 15 proteins significantly increased in IgAN glomeruli. A total of 7832 peptides were quantified, indicating the possibility of highly reproducible, large scale, quantitative analysis of FFPE kidney biopsy tissues. This powerful, fast and low cost tool for the examination of clinical FFPE specimens will be applicable in the future to obtain significant information from renal biopsy specimens, helping to gain insight into pathophysiological mechanisms and to refine diagnostic and prognostic evaluation.

Recurrent transient renal Fanconi syndrome: adverse effect of the artificial sweetener cyclamate

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Cyclamate is a widely used artificial sweetener. Although initially recognized as safe and rarely toxic, its main metabolite cyclohexylamine (CHA) can accumulate in kidney cortex and cause blader carcinomas in rat. We recently identified CHA as a selective effect of proximal tubule (PT) dysfunction in a previously healthy 6-year-old girl who experienced 11 episodes of transient renal Fanconi syndrome after consumption of cyclamate-containing drinks. In vitro analysis of CHA effects were performed in two PT cell lines: the immortalized opossum kidney (OK) cells which show high endocytic activity; and human primary PT cells (HRPTEpiC) to overcome limitations of immortalized cells. Confluent monolayers were treated for 24–48h with increasing concentrations of (10 nM to 1 mM) CHA. Cell viability (MTT assay) for both cell lines was down to 7 ± 4% after 24h incubation with 1 mM CHA, but was not affected by 100 nM CHA. The effect of CHA on the function of PT cells was assessed by monitoring the receptor-mediated endocytic uptake of labelled albumin. Compared to the uptake in control conditions (166 ± 7 ng/ug protein over 15 min), OK cells treated with 100 nM CHA showed a strong decrease in albumin uptake after 24h (31 ± 28 ng/ug protein over 15 min; p = 0.004) and 48h (26 ± 25 ng/ug protein over 15 min; p = 0.009), with stable cell viability. A similar, but milder decrease was observed in HRPTEpiC cells, that was related to a decreased expression of the multi-ligand endocytic receptor megalin. These data reveal that CHA may cause a transient PT dysfunction in vivo, with a selective defect in receptor-mediated endocytosis possibly due to decreased expression of megalin.
Oxygenation of the renal cortex: Computational modeling and anatomical Observations

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Kidney oxygenation is governed by the interplay between oxygen perfusion, oxygen consumption and arterial-to-venous oxygen shunting. In this work, a computational model of oxygen transport in the kidney cortex is developed in order to investigate the relationship between these three main contributors. Oxygenation dynamics are closely associated with vasculature structure. Available literature data on kidney vasculature is not sufficient for a thorough understanding of the oxygenation. In this work, the current state of the art is improved via micro computed tomography and scanning electron microscope observations of vascular corrosion casts of mouse kidneys. Focus is placed on the investigation of the vasculature structure down to the capillary level and determination of the spatial associations between preglomerular arterial and venous trees and the peritubular capillary network. Available PO2 measurements are taken as baseline and reproduced with the computational model. In a first observation, it is found that pure diffusional transport of oxygen between the arterial and venous vasculature cannot account for the available PO2 measurements. Here we propose a convection-dominated O2 shunting mechanism through the capillary network that fills the tissue between the arteries and veins. We further show using the corresponding computational model how altered renal blood flow, hemodilution and hypoxemia may affect kidney oxygenation.

Role of Sodium-dependent Phosphate Transport Protein 2C (NaPi2c) in Osteoclasts

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Mineral transport in osteoclasts has not been characterized to full extent, even if several calcium and phosphate transporters were shown to be expressed. Here, we hypothesized that the sodium-dependent phosphate co-transporter NaPi2c (SLC34A3) is playing a physiological role in bone turnover.

In vitro studies, as well as an in vivo mouse model were designed to gain further insight in osteoclast-mediated phosphate transport. In vitro and ex vivo: RAW 264.7 cells and freshly isolated bone marrow-derived monocytes (BBM) were differentiated to osteoclasts by RANKL stimulation. RNA was extracted at different time points and RT-PCR was performed using specific primers. Proteins were extracted and subjected to SDS-PAGE and Western blot. In vivo: An osteoclast-specific knockout mouse model for NaPi2c was established by crossing mice with floxed exons 4-12 of SLC34A3 with mice expressing Cre recombinase under the control of the promotor of cathepsin K. Genotype, gross anatomy and phenotype were studied, and RNA was extracted for qPCR.

Both RAW 264.7- and BBM-derived osteoclasts showed expression of Pit-1, Pit-2 and NaPi2c by RT-PCR, by contrast to NaPi2a and NaPi2b which were not detected. By Western blot, NaPi2c was also present in BBM, but NaPi2a was not. Overall, NaPi2c expression was maximal 5 days after culture and was lower after RANKL induction. In vivo: Homozygous NaPi2c floxed mice expressing the osteoclast-specific Cre are viable and show normal growth and weight compared to wildtype mice. Tooth development was also normal. NaPi2c is present in osteoclasts – in vitro and ex vivo. Its precise physiological role needs to be further investigated using osteoclast functional assays and in vivo bone and mineral assessment using the osteoclast-specific knockout mouse model.
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