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OC 01

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 cells 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.

OC 02

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 thrombopenia. 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 thrombopenia 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 positive for ATG and the complement fragments C1q, C3d and C5b-9. Also, ATG-induced MV activated thrombin in a dose-dependent manner *in vitro*. In a cohort of hematopoietic stem cell (n = 10) and kidney transplant patients (n = 9), treatment with both ATG Fresenius® or Thymoglobulin® resulted in rapid development of thrombopenia (153.5 ± 19.1 before vs. 105.5 ± 16.5 x10^9/l after infusion) and a significant increase of plasma d-dimer (2.3 ± 0.8 vs. 7.6 ± 1.5 μg/ml), thrombin-anti-thrombin-complex (10.3 ± 3.9 vs. 17.4 ± 2.7 μg/l) and sC5b-9 levels (260 ± 49.9 vs. 401.8 ± 58.4 ng/ml) at 24 hours compared to baseline.
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 thrombopenia, hypercoagulobility and systemic complement activation. We are currently in the process of patient plasma MV analysis.

OC 03

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- 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 immunoabsorption based on a fixed protocol, as well as six patients with either donor-specific HLA antibodies (n = 4) or with missing AB-secretor-status (n = 3). Thirthy 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.

OC 04

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

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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 being listed. Unknown patients with <90d follow up were excluded.
Results: 239 patients started RRT, 46% were known. Among the 128 unknown patients, 81 had a follow-up (FU) <90d leaving 47 for analysis.

	Known	**Unknown und FU>90d**
N	111	47
% males	66%	72%
Age	60 ± 15	62 ±18
Listed within 2y	52.3% (58)	**21.3% (10)****
Months to listing	2.4 ± 16	**10.1 ± 10***
*p <0.05, **p <0.001		

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.

	Listed without deferring	Deferred listing
N	59	16
Age	50 ± 14	**60 ± 13***
% males	71%	56%
% Known	78%	75%
Listed within 1y	86%	**19%****
Listed at any time	93%	**44%***
Months to listing	1 ± 15	**17 ± 11***
At end of FU		
– died	5%	19%
– ongoing	20%	**62%****
– transplanted	75%	**19%****
*** p <0.05, **p <0.001**		

Conclusion: Patients unknown to nephrology services are less frequently listed after 6 months RRT. Up to 1 in 5 suitable patient defers the process of wait-listing. Deferring patients loose a whole year and after 3 years a significantly lower proportion will be listed or transplanted. The best way to manage patients deferring waitlisting should be considered.

OC 05

Acute and six months mineral metabolism adaptation in living kidney donors: a prospective study

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Background: Following the evolution of living kidney donors (LKDs) is important to understand renal adaptation to renal mass reduction. In this prospective study, we follow mineral metabolism adaptation of LKDs over six months.
Methods: From May 2010 to December 2012, we included and followed 26 adults LKDs. 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)2D 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 FGF23in LKDs. This may in part explain their better cardiovascular prognosis.

Oral communications – Clinical nephrology / hypertension

OC 06

Albuminuria is associated to increased phosphate level independently of GFR

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Background: Albuminuria is associated to increased cardiovascular mortality. We hypothesized that albuminuria may directly decrease renal phosphate excretion leading to increased plasma phosphate and cardio-vascular risk.
Methods: In a cohort of 1835 CKD patients, a cross-sectional analysis was performed to correlate plasma phosphate level to albuminuria. Phosphate handling was analyzed in 6 nephrotic children during both proteinuric and remission phases. Animal studies were done in PAN-induced nephrotic rats and in transgenic proteinuric mice.
Results: In CKD patients, multivariate analysis demonstrates that albuminuria >300 mg is a predictor of plasma phosphate level, independently of GFR and other factors. Presence of albuminuria is associated to higher plasma phosphate, PTH and FGF23 levels independently of GFR. This association is most apparent for GFR <45 ml/min. In nephrotic children, plasma levels and tubular reabsorption of phosphate increased significantly during nephrotic compared to remission phase. Finally, in PAN-induced nephrotic rats under either normal or high phosphate diets, NaPi2a expression was increased in proteinuric animals compared to control despite elevated PTH and FGF23 levels. Klotho and p-FRS2 protein expression were decreased despite higher FGF23 levels. NaPi2a internalization in response to oral phosphate load was impaired in proteinuric animals. In genetically modified mouse presenting severe albuminuria and decreased GFR, NaPi2a expression was unchanged despite lower GFR.
Conclusions: Our observations in proteinuric adults, children and animals demonstrate a direct effect of urinary albumin on phosphate handling. This effect appears to be mediated by proximal tubule resistance to FGF23, leading to increased NaPi2a expression and phosphate reabsorption.

OC 07

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

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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.

OC 08

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-antigene 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 (t_0) and at protocol biopsies 3 & 6 months post-transplant (t_3 & t_6). Patients were treated according to standard IS regimen, i.e. induction with basiliximab or thymoglobuline 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 was 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 of IgA1 and Gd-IgA1 changed significantly according to the degree of IS (fig. 1 and 2).
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.

Figure 1

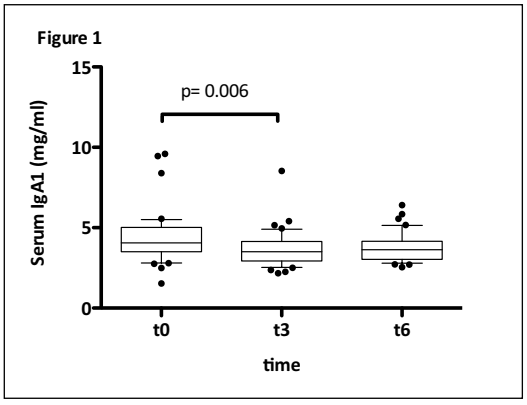
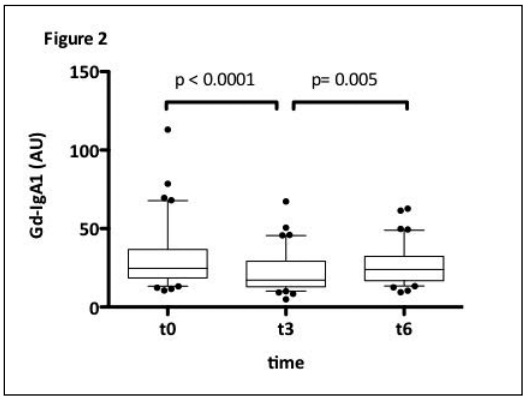


Figure 2



OC 09

Genetically high plasma angiotensinogen potentiates L-NAME induced Hypertension and promotes cardio-vascular end-organ damage in transgenic rats

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Objective: Genetically high plasma angiotensinogen (Agt) has been associated with elevated blood pressure (BP) in humans. It may increase the susceptibility to exogenous BP stressors. To test this hypothesis, transgenic rats (TGR) with high plasma (Val^5)-Agt were treated with L-NAME.
Methods: Heterozygous male TGR and normal control rats (CTR) aged 10 weeks received 30 mg/kg body weight (BW) L-NAME or vehicle (n = 8/group) for 3 weeks. Blood pressure (BP) was measured before and at the end when heart weight (HW), BW, plasma Agt and aldosterone and urinary (u) concentrations of Na, K, creatinine and protein were determined. Kidney mRNA (rt-PCR) was quantified for endothelin-1 (ET), renin (REN), Agt, AT_1-receptor, fibronectin (FIB), collagen-1, -4, transforming growth-factor β, NADPH-oxidase units $phox^{47}$ and gp^{91}, and cardiac collagen-4 and Ang converting-enzyme.
Results: Plasma Agt was ~7 times higher in TGR. Baseline BP was +24 mm Hg, u-protein 6.9-times, uNa and uNa/creatinin 1.8-times, HW/BW 1.2-times higher, kidney ET-mRNA was 1.8-times (p <0.05 all) and plasma aldosterone 1.5-times (p = NS) higher vs. CTR; uK was 0.6-times (p = NS) and REN-mRNA expression was 0.35-times lower vs. CTR (p <0.05) without differences for the other genes (p = NS). L-NAME increased BP by 36% in TGR vs. 25% in CTR, HW/BW (16% vs. 2%), plasma aldosterone (51% vs. –13%; all p <0.05). It decreased TGR uNa and uNa/creatinin (~40%), CTR kidney REN-mRNA expression (-42%, p <0.05), and increased CTR u-protein (10-times) and TGR kidney FIB and $phox^{47}$ mRNA (+55%, +26%, p <0.05) without significant other differences (p = NS).
Conclusion: Genetically high plasma Agt levels increase local Ang II stress, potentiate L-NAME-induced hypertension and synergistically promote end-organ damage compared to normal Agt levels.

OC 10

Leptin is associated with nighttime sodium excretion: a cross-sectional study in an African population

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Background: Leptin is considered as key factor in obesity-related hypertension. In animal studies, leptin has been shown to induce natriuresis. The objective of the study was to analyze the association between leptin levels and sodium excretion.
Design and methods: This cross-sectional study was conducted in 365 participants of African descent with positive family of hypertension. Participants' baseline demographics, ambulatory blood pressure, daytime and nighttime urinary collection and laboratory data including leptin were measured using standard techniques. We used Pearson's correlation to test the association followed by multiple linear regression to account for potential confounders.
Results: Mean age ± standard deviation (SD) and body mass index (BMI) were respectively 46.6 ±11.8 years and 27.7± 4.9 kg/m^2. 57% of participants were women and 60% had hypertension. Mean leptin concentration ± SD was higher in women (32.8 ± 1.9 ng/ml vs 8.0 ± 0.5, P <0.001) and increased across BMI categories (normal, overweight, obese, respectively 10.4 ± 10.5 vs 20.1 ± 14.4 vs 37.7 ± 37.9 ng/ml, P <0.001). Leptin was associated with nighttime fractional excretion of sodium in univariate (r = 0.16, P <0.01) and multivariate linear regression analysis (β coefficient = 0.07, P = 0.017) independently of sex, age, BMI and nighttime systolic blood pressure. No association was found between leptin and daytime fractional excretion of sodium.
Conclusion: Leptin is associated with higher nighttime sodium excretion in this African population. Leptin may be an important factor in the abnormal pressure-natriuresis relationship seen in obesity-related hypertension.

OC 11

Prevalence and predictors of sleep apnea in patients undergoing chronic intermittent hemodialysis

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** 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 SDB 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 SDB 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.

OC 12

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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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.

OC 13

Walking capacity improves survival in a large prospective Swiss dialysis cohort

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Purpose: Previous studies revealed an association between physical activity and mortality in hemodialysis (HD) pa-tients. 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.: 1.2–9.8) 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.

3MWT, m	Age, yr	CCI *	Hosp per yr, d	Time on HD, yr	UBS, kg	24-hour step count
Low	74 ± 11	4.5 ± 2	23 ± 42	4.3 ± 5	18 ± 9	2080 ± 2098
High	63 ± 16**	3.6 ± 2**	11 ± 28**	4.2 ± 4	27 ± 13**	5400 ± 3996**
*) Charlson comorbidity index; **) P <0.001 vs. "low 3MWT"						

OC 14

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 medial 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 sphygmomanometer on the brachial artery.

Methods: The aim of the study was analysing whether PWV obtained by PWA better differentiates the dialysis population from a control group of matched non-CKD patients than PP. A cohort of 143 patients from 4 different dialysis units has been followed since January 2011 measuring PWV every 6 months.
Results: PWV discriminates better the dialysis population from the control group than PP. The increase in PWV was more rapid in the dialysis group and accelerated with age. 13.3% of the dialysis patients were outliers for the PWV but none in the control group. The mortality rate (16 out of 143) was similar in outliers and inliers (7.4 and 8.0%/y). Stratifying patients for PWV a significant difference in survival was seen. To be dialysed for a hypertensive nephropathy correlated to a higher baseline PWV. The progression of PWV in dialysis did not significantly differ from the rate expected. A high PTH correlated to a higher baseline PWV.
Conclusions: Estimating PWV by PWA on the brachial artery is a valid and simple alternative to direct measurement and discriminates better the dialysis population than PP. As demonstrated in previous studies arterial stiffness correlates to mortality. Among specific CKD risk factors only PTH correlates to higher baseline PWV.

OC 15

Efficient Removal of β2-Microglobulin and Leptin by Online Hemodiafiltration: Comparison of Three State of the Art Dialyzers

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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 (oHDF) 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/' blood flow, 800 ml/' dialysate flow and 80 ml/' (19.2 L/4h) substitution rate. The dialyzer used was in randomized order a FX100, Polyflux 210H (PF210) or a FXCorDiax100 (CorDiax) dialyzer. Arterial samples were taken at oHDF start (t0), at 60 and 240 minutes (t60/t240) and 30 minutes after the end (t270). Blood side clearances were computed at t60 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.
Conclusions: oHDF with modern highflux dialyzers removes significant amounts of ß2M and lowers plasma leptin, with no relevant albumin loss. The CorDiax dialyzer in these real-life conditions performed better than the two other dialyzers.

		PF210	FX100	CorDiax
Leptin	**eRR (%)**	26.7 ± 23.0	39.2 ± 21.7[p]	40.6 ± 27.5[p]
	Clearance 240 (ml/min)	89.7 ± 19.2	102.8 ± 20.4[p]	110.8 ± 13.4[p]
ß2M	**eRR (%)**	62.7 ± 5.3	67.9 ± 5.0[pf]	72.3 ± 5.3[pf]
	Clearance 240 (ml/min)	115.5 ± 9.8	136.3 ± 12.8	150.4 ± 10.9[pf]
	Dialysate removal (mg/4 h)	191.0 ± 67.8	204.9 ± 62.4	215.1 ± 63.3[p]
Albumin	**Dialysate loss (g/4 h)**	1.31 ± 0.12	2.10 ± 1.00[p]	1.74 ± 1.01
[p] p <0.001 vs. PF210 [f] p <0.001 vs. FX100				

Oral communications – NCCR / experimental nephrology

OC 16

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/lithium countertransporter which was epidemiologically linked to the pathogenesis of diabetes mellitus and essential hypertension. We recently demonstrated that NHA2 is critical for insulin secretion in β–cells (Fuster et al., *PNAS* 2013). Here we find that NHA2 is expressed in distal convoluted tubules of mice and humans, a tubular segment that is paramount for the regulation of sodium, calcium and blood pressure homeostasis. To test the physiological role of NHA2 in the kidney we performed telemetric blood pressure measurements and metabolic balance studies in NHA2 WT and KO mice. NHA2 was dispensable for the renal adaptation to acute metabolic acidosis and water deprivation. Blood pressure, however, was lower in NHA2 KO mice compared to WT mice under high sodium diet but not under low sodium diet. In addition, NHA2 KO mice exhibited normocalcemic hypocalciuria with lower plasma PTH levels while 1, 25-OH Vitamin D3 levels remained unaltered. Interestingly, immunoblotting of kidney tissue lysates revealed significant downregulation 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.

OC 17

Ureteric 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 ureteric 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 ureteric 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 and immunohistochemistry analyses showed increased levels of Rb1cc1, Arkadia1, and phosphorylated Smad3 and decreased levels of Smurf2, Smad7, 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, whereas the addition of TGF-b1 accelerated the suppression of UB branching in organ cultures of both isolated UBs and whole embryonic kidneys. Considering these results, we conclude that UB branching is suppressed through increased activation of the TGF-β/Smad3 signaling pathway when Trps1 is lost.

OC 18

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 cathepsin K promoter to generate osteoclast-specific NCX1 knock-out mice (herein named NCX1 $^{\Delta OC/\Delta OC}$ mice). Osteoclasts differentiated from NCX1 $^{\Delta OC/\Delta OC}$ 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 $^{\Delta OC/\Delta OC}$ osteoclasts. NCX1 expression was unaltered in extraosseus tissues in NCX1 $^{\Delta OC/\Delta OC}$ in 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 $^{\Delta OC/\Delta OC}$ mice. Similarly, no differences were observed when we assessed osteoclast differentiation or bone resorption in vitro of cells isolated from wild-type and NCX1 $^{\Delta OC/\Delta OC}$ mice, respectively. Finally, to stimulate osteoclast-mediated bone resorption, we performed surgical ovarectomy in 12 week old female mice. Ovarectomy-induced bone loss, however, was identical in wild-type and NCX1 $^{\Delta OC/\Delta OC}$ mice at 3,6, 9 and 12 weeks after the operation.
Conclusion: Thus, our data indicate that genetically induced deficiency of NCX1 in osteoclast-precursors and mature 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 ovarectomy-induced bone loss in female mice until 12 weeks after the operation.

OC 19

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 make 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 kidney. 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.

OC 20

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 and crystalline spindle-shaped, respectively. CPP-I 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-1β 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 inflamma.

P 01

Generation of angiotensin-receptor and anti-perlecan antibodies: allo- or autoimmunity?

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Non-HLA antibodies against the angiotensin II type-1 receptor (AT_1R) and the C-terminal fragment of perlecan (i.e. LG3) are associated with the development of renal allograft rejection. It is currently unknown, how humans develop AT_1R or anti-LG3 antibodies. The aim of this study was to investigate whether pregnancy – as a model of sensitization to polymorphic proteins – induces AT_1R and/or anti-LG3 antibodies. We included 104 samples from women obtained after a full-term pregnancy and 80 samples from healthy controls (40 females, 40 males). Both AT_1R and anti-LG3 antibody levels were lower in pregnancy samples than in controls (both $p < 0.05$). By multivariate analysis, male gender was an independent predictor for high AT_1R antibody levels (OR 3.66; $p = 0.04$), and pregnancy was predictive for low anti-LG3 antibody levels (OR 6.75; $p < 0.0001$). There was no correlation of AT_1R with anti-LG3 antibody levels, neither in the pregnancy nor in the control samples ($r^2 \leq 0.03$; $p \geq 0.25$). In conclusion, full-term pregnancy does not induce AT_1R - or anti-LG3-antibodies, and may even lower their levels. Therefore, AT_1R and anti-LG3 antibodies are not caused by allosensitization, but likely represent an autoimmune response. The lacking correlation of AT_1R and anti-LG3 antibodies suggests different mechanisms of generation which remain to be elucidated.

P 02

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 at the University Hospital of Basel between 2000 and 2011 are investigated. A standardized questionnaire is used. Information about education, employment, relationship, family status, and quality of life 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 or the number of transplantations is detectable.

Established work situation before and after transplantation:

n = 316 replying patients	1 year before transplantation	1 year after transplantation
retired	53 (17%)	63 (20%)
working	149 (47%)	137 (43%)
disability pension	47 (15%)	53 (17%)
working + disability pension	31 (10%)	26 (8%)
house work	17 (5%)	11 (3%)
unemployed	3 (1%)	9 (3%)
other (part time job, students, no details etc.)	16 (5%)	17 (5%)

Breakdown of patients' answers about improvement of life:

n = 316	No	Yes	uncertain
Improvement of life with transplantation	12 (4%)	271 (86%)	33 (10%)

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, Berne, Geneva, Lausanne and Zurich) 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 be-ing 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-er, 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 assessments.
In a multivariate model, Hb was no longer a significant predictor for death and graft loss.
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.

Outcome at follow-up (2012) based on baseline anemia status and ESA usage, respectively, and clinical characteristics (2008).

	Hb <11 g/dl N = 204	Hb ≥11 g/dl N = 790	P	With ESA N = 197	Without ESA N = 819	P
Hb, g/dl	9.9 ± 0.9	12.9 ± 1.3	0.000	10.9 ± 1.4	12.6 ± 1.6	0.000
On ESA, %	48.0	12.4	0.000			
Ferritin, µg/l	379 ± 392	227 ± 264	0.000	378 ± 372	226 ± 271	0.000
GFR, ml/min	40 ± 20	50 ± 19	0.000	34 ± 21	51 ± 18	0.000
λ GFR	–1.6 ± 20.7	–2.4 ± 15.0	ns	–3.7 ± 23.3	–2.0 ± 14.2	ns
CRP, mg/ml	12 ± 26	6 ± 16	0.001	9 ± 17	7 ± 19	ns
iPTH, ng/l	126 ± 91	106 ± 128	ns	129 ± 99	106 ± 128	0.050
Graft loss, %	16	5	0.001	22	4	0.000
Patient death, %	16	6	0.000	16	7	0.001

P 04

Serum CXCL10 chemokine and correlation with subclinical vascular rejection

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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, endothelialitis, and peritubular capillaritis). 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 with the exception of a slightly elevated acute i-score and concomitant Polyomavirus BK (BKV) or Cytomegalovirus (CMV) viremia (n = 18), (iii) tubulitis t1-3 (n = 16), 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 = 0.003 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.

P 05

Excellent allograft survival (and improvement of lung function parameters) in patients receiv-ing kidney after lung transplantation

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In the last decade a new population appeared on the waiting-list for kidney transplantation (KiTPL). The group of recipients of a non-renal transplant eventually reaching ESRD is growing. However the course after kidney transplantation in this particular group of patients is barely reported in literature.
The goal of our examination was to characterize the course of renal allograft function, lung function and changes of donor-specific anti-HLA-antibodies in patients receiving kidney after lung transplantation (LuTPL).
We describe a group of 13 patients (mean age 44.58 years; 5 females) who received KiTPL after LuTPL at the University hospital in Zurich between 1995 and 2011. Renal transplantation (10/13 with living donation) was performed at a mean of 8.75 (± 2.3) years after LuTPL. The mean follow up after KiTPL was 48 (±24) months. Renal allograft function was estimated with MDRD equation and lung function was assessed by forced expiratory volume in first second (FEV1) in follow-up visits every month. Anti-HLA antibody screening was performed with luminex® before and after any transplantations.
The renal allograft survival two years after KiTPL was 100%.
12 months after KiTPL we found a mean eGFR of 58.3 ml/min (±24.0) and 24 months after KiTPL an eGFR of 55.8 ml/min (± 20.6). None experienced a rejection in this time period. In the first 12 months after KiTPL 7 showed in increase and 5 a decrease of FEV1 (mean change +124 ml (SD354), one person remained stable. For the period of the first 24 months after KiTPL 5 showed an increase in FEV1, 3 a decline and 2 remained stable (mean change –74 ml (SD 462)). No patient showed a new positivity in Luminex® screen both after LuTPL and KiTPL.
We found an excellent outcome of renal and pulmonary function in the first two years after kidney transplantation in lung transplant recipients.

P 06

Late antibody-mediated rejection and Transplant glomerulopathy: how to avoid Chronic rejection?

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Immunosuppressive regimen fine tuning as well as anti-HLA antibodies follow-up have improved acute antibody mediated rejection (AMR) management. In contrast, long-term graft outcome may be worsened because of a delay in the diagnosis.
In our 850 kidney transplant recipient cohort between 1983 and 2013, we observed de novo anti-HLA antibody in 41 patients (4.8%), among which 31 had de novo DSA (81%). 5 had anti-HLA class I only, 19 had class II only and 7 had class I and class II. These data correlate with a previous report. We observed a 100% patient and graft survival at 30 years and 15 years respectively. As in many transplant centers, our patients had yearly follow-up with graft biopsy performed upon decreased renal function or de novo anti-HLA antibodies. Among the 31 patients with DSA, we observed 13 patients with late rejection (>1 year), 7 with acute rejection and 4 with both, acute followed by late rejection (<6 months). All patients with late and acute/late rejections had a graft biopsy performed. We found 13 humoral, 2 cellular and 2 mixed rejections. The 2 pure cellular rejections were observed in patients with late rejection only and the 2 patients with a mixed rejection had an acute/late rejection. All diagnosed rejections were successfully treated with plasmapheresis, rituximab and corticoid pulses. To note, these patients were treated for rejection even with normal range creatinine. So far we did not observe graft loss due to late rejection episode indicating that late humoral rejection has to be treated in order to avoid late complication with TG. We also have to determine how often anti-HLA antibody analysis has to be performed to define its prognostic value, and therefore prevent TG and its poor prognosis.

P 07

Urinary stone disease after kidney transplantation: how we manage it

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Introduction: Over the past decades, prevention, diagnosis and therapy of urinary stone disease (USD) in the setting of preserved autologous kidney function have been subject to great development. On the contrary, little is known about prevention and management of USD after kidney transplantation, given by the relative low incidence.
Methods: We retrospectively analyzed data from 11 patients with clinically relevant USD after KT in a Swiss tertiary hospital. All patients were assessed at our multidisciplinary uro-nephrological board between 1998 and 2003.
Results: Median age at KT 49 (30-69). Male:female 5:6 ratio. Mean time to diagnosis of transplant-USD 31 months (2-110). Condition leading to diagnosis of transplant-USD: recurrent urinary tract infection for 7 patients (64%), microhematuria for 3 patients (27%) and incidental finding for 1 patient (9%). Five patients had a concomitant secondary or tertiary hyperparathyroidism. Only one patient had a past episode of USD prior to transplantation. Therapy for ureteral stones was Extracorporeal shockwave lithotripsy (ESWL) (4/5) or conservative management (1/5), whereas kidney stones were treated by ESWL (3/9), ureterorenoscopy (URS) (2/9), ESWL and URS (1/9) or conservatively (3/9). In Sum, 8 patients had an active therapy for ureteral and/or kidney stones, 5 of which remained infect-free to date and only 1 patient had a documented stone recurrence (mean follow-up 48.5 months).
Conclusion: Secondary and tertiary hyperparathyroidism are frequent comorbidities after KT and make those patients prone to USD. As a consequence, USD has to be ruled out when facing recurrent urinary tract infection or microhematuria after KT. Finally, active surgical approach appears to be an adequate therapy when indicated.

P 08

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, 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-7, 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.

Poster presentations – Clinical nephrology, hypertension and case reports

P 09

Recurrent bone fractures due to tenofovir induced renal phosphate wasting

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Tenofovir disoproxil fumarate is a nucleoside reverse transcriptase inhibitor which is widely used against human immunodeficiency virus (HIV) and hepatitis B virus. We present a 42-year-old HIV-infected man, who suffered from several stress fractures five years after starting tenofovir treatment. Osteomalacia was confirmed with an isotope bone scan. Laboratory examination revealed severe hypophosphatemia due to heavy renal phosphate wasting. Renal biopsy revealed tubular necrosis with characteristic nuclear changes and giant mitochondria on electron microscopy. Cessation of tenofovir treatment led to normalization of the electrolyte disorder. Several cases of proximal tubular dysfunction have been described due to tenofovir treatment. However, more attention has to be paid on monitoring serum phosphate and alkaline phosphatase levels, since tenofovir-related renal phosphate wasting increases the risk for bone fractures.

P 10

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

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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 poisoning was diagnosed (serum level 2.15 mmol/L, therapeutic range 0.5–1.0 mmol/L). GFR (CKD-EPI) was 43 ml/min/1.73 m^2; Lithium was stopped. After rehydration, the patient was transferred to a psychiatric clinic with a lithium level of 1.03 mmol/L. 3 days later she was referred due to polyuria, GCS 10, severe rigor of both arms and hypothermia. She had a GFR 4 ml/min/1.73 m^2, with fractioned excretion of urea >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. The Lithium blood level was <0.10 mmol/L. 3 weeks later she was in good physical condition. GFR was 41 ml/min/1.73 m^2, suggesting a TIN as the consequence of her long-term lithium intake.
Discussion: Lithium poisoning at therapeutic serum levels has been reported. And patients with elevated serum levels have been found without any signs of intoxication. It has been shown by MRI spectroscopy that neurotoxicity probably correlates better with the lithium level in the brain than with blood levels. 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.

P 11

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

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Introduction: Mycobacterium haemophilum is a nontuberculous mycobacterium (NTM) which rarely causes localized or disseminated disease in immunocompromised hosts.
Case report: A 65-year-old patient with renal transplantation 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 m^2) 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 and acid fast bacilli (AFB). Empiric antituberculotic therapy with rifampicin, isoniacid and pyrazinamid was started. Finally M65myco-PCR of a skinbiopsy was positive and confirmed M. haemophilum infection. After one week of treatment we switched to rifampin, clarithromycin and moxifloxacin for one year. The patient completely recovered except for a skin lesion on the cheek. Repeated skin biopsy showed no reliable evidence of AFB. After one year of follow-up there are 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.

P 12

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 from Raynaud's phenomenon in both hands. Five fingers showed signs of beginning digital necrosis. The patient developed renal failure.
Clinical Examination and Laboratory Examination: Heart rate was 112 bpm and RR 110/70. C-reactive protein (CRP) was elevated with 107 mg/l, S-Cr 262 µmol/l, albumine 33 g/l, hemoglobin 113 g/l, erythrocyte sedimentation rate 82 mm/h. Proteinase 3 Antineutrophil Cytoplamic Antibodies (PR3-ANCA) were elevated to 75 U/ml (<5), MPO-ANCA were normal; Renal biopsy revealed pauci-immune glomerulonephritis with crescents in 5 of 11 glomerula.
Course: We diagnosed an ANCA-associated vasculitis with involvement of the kidneys and the fingers. We started a treatment

with pulses of intravenous methylprednisolone and oral cyclophosphamide leading to an improvement of the kidney function, but no improvement of the lesions of the fingertips despite 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 continousliy.
Conclusion: Raynaud's phenomenon and digital necrosis should include the differential diagnosis of ANCA associated vasculitis.

P 13

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

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**Equal contribution*

Metamizol is analgesic, anti-pyretic pyrazolone derivative, and non narcotic. Elimination is at 60% by kidney. Recently two unknown metabolites were found: the arachidonoyl amides (4 methyl amino antipyrine and 4-aminoantipyrine) which were positively tested for cannabis receptor binding (CB1 and CB2) and cyclooxygenase inhibition (COX-1 and COX-2), suggesting that the endogenous cannabinoid system may play a role in the effects of dipyrone against pain. It is used often to treat postoperative pain, colic pain, and cancer 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.

P 14

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 kidney biopsy which showed hypertensive nephropathy and, surprisingly, oxalate nephropathy. The past medical history revealed a gastrectomy due to a neuroendocrine carcinoma of the stomach. Later a diabetes mellitus developed. 24-h urine analysis showed severe hyperoxaluria and stool analysis absence of pancreatic elastase. Abdominal ultrasound confirmed atrophy of the pancreas. Gastroscopy revealed bacterial overgrowth. He was treated with Metronidazole 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 aethylenglycol 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.

P 15

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 iboprufen. The patient felt feverish. 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 399 µmol/L. The urine showed 7 leucocytes /hpf, 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 iboprufen. 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 microhaematuria developed, a urinary culture for ureaplasma urealyticum, mycoplasma hominis and a PCR for neisseria gonorrhoe and chlamydia trachomatis were performed. There was growth of ureaplasma urealyticum (>10 000 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 hypothesize that bilateral ureteritis led to transitory ureteric obstruction and renal failure.

P 16

Allele-specific human leukocyte antigen alloantibody 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 screening by single antigen beads for class I and II revealed only one positive bead defined by an MFI >500. The antibody reacted only with the A*02:01 bead (MFI 650), while the A*02:03 and A*02:06 beads were negative. This anti-A*02:01 antibody was donor-specific by virtual 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/steroids 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.

P 17

Successful treatment of a pacemaker infection with intraperitoneal daptomycin dosed according to systemic serum drug concentrations

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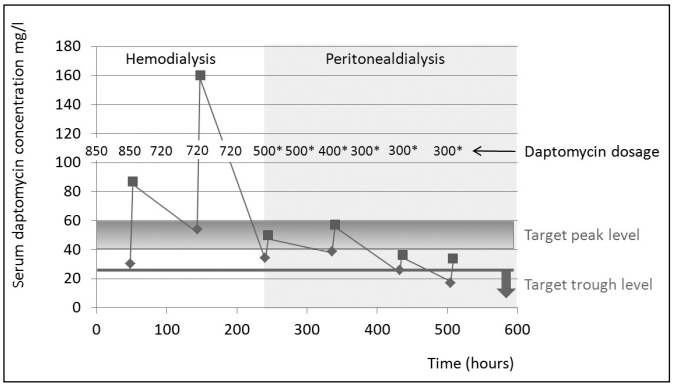
A 54-year old female patient on long-term hemodialysis developed sepsis after insertion of a pacemaker for the treatment of symptomatic 3rd degree heart block. In four out of four blood culture bottles grew *S. epidermidis* sensitive to daptomycin (minimum inhibitory concentration 0.25 mg/l). Due to thrombosis of the superior vena cava, the pacemaker system could not be explanted and an extensive course of antibiotics was required. Intravenous daptomycin was commenced at 9 mg/kg body weight (850 mg) after every dialysis three times weekly. Hemodialysis was then switched to peritonealdialysis 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 mg are given on the graph. The blue rhombuses denote trough serum concentrations and the red squares the peak concentrations 4h hours 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 mg/l and a trough concentration (Cmin) <24 mg/l. Trough concentrations above 24 mg/l (horizontal blue line on the graph) are known to be associated with increased muscle toxicity which is why this target Cmin of <24 mg/l was set. Ultimately the patient could be successfully treated with 300 mg 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 mg/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.



P 18

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

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Background: Atypical hemolytic uremic syndrome (aHUS) is associated with mutations in genes coding for complement regulatory proteins. Thrombotic microangiopathy (TMA), the hallmark of aHUS recurrence after renal transplantation, often leads to graft loss. Until recently, isolated *CD46* (MCP) mutation was not considered as high recurrence risk after renal transplantation.
Case report: A 37-year-old woman, dialyzed for aHUS (isolated *CD46* mutation), underwent deceased donor kidney transplantation. Immunosuppression consisted of basiliximab induction, tacrolimus, mycophenolate mofetil and corticosteroids. Renal function went immediately well with corticosteroids withdrawal at 1 year post transplant. At 15 month, she had a miscarriage followed by a Banff I A rejection treated with methylprednisolone and thymoglobulins leading to full recovery. At 35 months, a preeclampsia was diagnosed with peripheral and graft TMA leading to prompt delivery and tacrolimus withdrawal. Serum creatinine returned to baseline 2 weeks later. 5 years post-transplant while under tacrolimus, azathioprine and prednisone, she presented a viral nasopharyngitis followed, 3weeks later, by acute oliguric renal failure. Complement profile was normal and graft biopsy showed a C3GN described as postinfectious leading to methylprednisolone pulses. No improvement led to a new biopsy 3 weeks later that showed severe TMA; weekly eculizumab was 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).
Conclusion: C3GN can be the recurring phenotype of aHUS after renal transplantation. Identifying at risk SNP carriers may help to stratify recurrence risk and the use of prophylactic eculizumab.

P 19

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 fibrillary or immunotactoid 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 nephrotoxicity 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.

P 20

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 short 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 intraoperatively plasma infusion during the anhepatic phase to provide functional factor H and 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. Her 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.

P 21

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 months later, after the patient had already been listed for re-transplantation, she presented with fatigue, fever and night sweat. Her blood tests were normal except of a remarkable eosinophilia. Common underlying causes such as drug or allergic reactions as well as parasitic or myeloproliferative diseases were carefully excluded. Eventually, allograft rejection after immunosuppression minimization was considered as a rare potential cause of eosinophilia. Consequently, immunosuppressive therapy was intensified, and eosinophilia improved. Shortly thereafter, the patient received her second transplant, and the first graft was removed simultaneously. Histologically the explanted kidney showed glomerulosclerosis in a segmental and global pattern, consistent with recurrent focal segmental glomerulosclerosis, diffuse interstitial fibrosis and tubular atrophy, diffuse interstitial inflammation with abundant eosinophils, chronic active T-cell mediated rejection with severe intimal fibrosis and arteritis with prominent eosinophils.
After graft nephrectomy, the patient recovered completely, and eosinophilia disappeared.
Thus, transplant physicians should be aware of systemic eosinophilia resulting from eosinophil-rich tubulointerstitial and vascular allograft rejection.

P 22

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 primarily in immunocompromised hosts, most often by reactivation of a previous latent infection. While BKV mainly affects the genitourinary tract, JCV may cause Progressive Multifocal Leukoencephalopathy (PML).
Patients: A 54-year-old man with polycystic kidney disease was transplanted in 2005. After two episodes of rejection, in 2009 renal function declined and renal biopsy showed a polyomavirus nephropathy. JCV, but not BKV, was found in serum. The immunosuppressive therapy was changed from Mycophenolate to Leflunomide, but JCV-PCR is still detectable (2300 GEq/mL) and current serum creatinine is 274 umol/L.
A 44-year-old man with IgA nephropathy and subsequent renal transplantation (2002) underwent a biopsy of the transplanted kidney in 2007, because of deterioration of the renal function. The histology showed tubular damage typical for polyomavirus nephropathy, associated with a high JC viremia, but negative BKV-PCR. Although Mycophenolate was changed to Azathioprine, JCV-PCR remains positive (901 GEq/mL) and latest serum creatinine is 489 umol/L.
Results: Both patients had a worsening of renal function caused by polyomavirus linked to high JC viremia, without detectable BKV-PCR. Nevertheless signs of PML are not detectable at cerebral MRI.
Conclusions: In rare cases biopsy-proven polyomavirus nephropathy may be caused by JCV infection without concomitant BKV. In such patients JCV creates similar lesions as BKV, in absence of cerebral involvement. In literature other few similar cases have been described and seem to have a better prognosis, but systematic studies are lacking.

P 23

A new mutation in CLCN5 causing Dent's disease and its clinical expression

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Dent's disease is an X-linked recessive disorder characterized by tubular proteinuria, hypercalciuria, nephrocalcinosis/nephrolithiasis and chronic renal insufficiency. Mutations in the CLCN5 gene have been identified in approximately 60% of cases. Here we describe a new mutation and the clinical characteristics of two affected brothers.
Case 1: A 35 year old man was referred because of bilateral nephrocalcinosis, nephrolithiasis and CKD3A. One of his two brothers 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 (p.G88Rfs*97).
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 infiltrates. A diagnosis 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.

P 24

Anti-GBM disease and the nephrotic syndrome

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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 hypalbuminemia (23 g/l). 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 small 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(IV)NC1 antigen.
Conclusion: The anti-GBM antibodies in this case were not directed against the α3 chain of collagen IV but against some unknown glomerular antigen. This may explain the unusual manifestation as membranoproliferative glomerulonephritis with the nephrotic syndrome.

P 25

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, hypothyreosis, 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 bone biopsy was performed. Bone histomorphometry demonstrated low bone turnover disease (LBD) as the underlying bone pathology. We started an osteoanabolic therapy with Teriparatide over a period of 18 months. A second DXA-Scan was performed, showing an impressive improvement in bone mineral density (BMD) of 22% in the lumbar spine and 4.3% in the femoral head respectively (table 1). No fragility fractures occurred during follow up.
Discussion: Recombinant PTH, given by daily subcutaneous 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
Results of bone density scans 2010 and 2012.

	DEXA 2010	DEXA 2012
LWS T-Score (SD)	–3	– 1.5
Schenkelhals T-Score (SD)	–2.7	– 2.5
Tibia Diaphyse T-Score (SD)	–1.8	– 2.9
Tibia Epiphyse T-Score (SD)	–2.7	– 3
Radius T-Score (SD)		– 0.6

Table 2
Blood results March 2010, February 2011, August 2012 (before, during, after therapy).

	March 2010	February 2011	August 2012
PTH (15–65 pg/mL)	58	72	67.2
25-Hydroxy-Vit D3 (49–134 nmol/L)	50	40	63
1,25-Dihydroxy-Vit D3 (48–160 pmol/L)	<12	47	32
Osteocalcin (<42 ng/mL)		131.5	25.7
beta-CrossLaps (<600 pg/mL)		1426	335

1 Daniel Cejka, et al. Treatment of Hemodialysis-associated Adynamic Bone Disease with Teriparatide: A Pilot Study. Kidney Blood Press Res. 2010;33:221–6.
2 Daniel Cejka, et al. Effect of Teriparatide on early bone loss after kidney transplantation. American Journal of Transplantation. 2008;8:1864–70.

P 26

Prevalence and risk factors for chronic kidney disease in a rural region of Haiti

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Background: In the carribean region chronic kidney disease (CKD) is an increasing challenge. High rates of non-communicable and infectious diseases and the rise in people suffering from diabetes and hypertension explain the observed and further expected increase of CKD. Early detection and prevention of renal disorders is the only realistic strategy to prevent an aggravation of the existing health and economic crisis and to encourage equity in health care.
Methods: In this single center prospective observational study adult patient visiting the medical outpatient clinic of Hôpital Albert Schweitzer (HAS) in Deschapelles Haiti were included in the study. We measured blood pressure (BP), body mass index, proteinuria by dipstick test, estimated glomerular filtration rate (eGFR by MDRD equation) using creatinine levels based on one random measurement and performed urinary sedimentation. Renal risk factors were assessed by a questionnaire.
Results: The prevalence of CKD in this study was 21.9%. 12.5% had CKD stage 1, 3.9% stage 2, 4.1% stage 3, 0.5% stage 4 and 0.6% stage 5. Proteinuria >30 mg/dl by dipstick test was found in 19.7%. The risk factors independently associated with CKD and proteinuria were hypertension and HIV infection. The prevalence of hypertension and Diabetes mellitus was high with 49.2% and 36.3% respectively. Only 59.9% of patients with known hypertension had their blood pressure controlled to less than 140/90 mm Hg at study visit.
Conclusion: The prevalence of CKD as well of the traditional risk factors for CKD is very high in Haiti. In addition this study provides evidence that CKD screening by urine dipstick test is a feasible option in countries with high prevalence of persons with CKD risk factors for the detection of patients at risk for ESRD.

P 27

Undergoing a renal biospy: How bad is it?

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Little is known about patients' perception of renal biopsy. Therefore we measured pain associated with the procedure and assessed complications both in native kidney biopsies and in renal allograft biopsies including surveillance biopsies. We investigated known risk factors for the development of complications in renal biopsies.
Methods: Between 01.01.07 and 31.12.12, 588 consecutive native and allograft kidney biopsies were performed at our unit. We prospectively assessed pain on a visual analogue scale (VAS) and recorded complications and patient characteristics from patients' charts at time of biopsy.
Results: Major complications occurred in 4% of native kidney biopsies and 1% of allograft biopsies. None of the investigated risk factors was significantly associated with complications.
Pain during biopsies was low and similar for both native and allograft kidney biopsies (VAS 1.8 ± 1.9 vs. 1.7 ± 2, p = NS). There was no significant difference in pain during biopsies between surveillance allograft biopsies and indication allograft biopsies (VAS 1.9 ± 2.1 vs. 1.6 ± 1.9, p = 0.21). We found a significant correlation between unsuccessful punctures and pain during the procedure both in native kidney and renal allograft biopsies (VAS 2.2 ± 1.8 vs. 1.6 ± 1.9, p = 0.002 and 2.1 ± 2.2 vs. 1.6 ± 2, p = 0.02.). In native kidney biopsies, patients with complications had significantly higher VAS after the procedure compared to patients without complications (VAS 1.1 ± 1.6 vs. 0.4 ± 0.9, p = 0.02), while in allograft biopsies there was no difference.
Conclusion: With a standardised information and procedure kidney biopsies including surveillance biopsies are safe and not burdening for the patient. Pain during the procedure is similar to periodontal probing.

P 28

Urinary uromodulin as a marker of renal function and mass: data from a population-based study. Based study

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Introduction: In genome-wide association studies, the *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 the loop 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, Geneva 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. Renal length (113 ± 8 versus 107 ± 7 mm), renal volume (154 ± 31 vs. 121 ± 28 ml), eGFR (101 ± 17 vs. 97 ± 16 ml/min/1.73 m²), mGFR (140 ± 35 vs. 113 ± 28 ml/min) and UER (46 ± 25 vs. 42 ± 19 mg/24h) were all higher in men than in women. In multilevel linear regression analysis, adjusted for center, age, gender, body height and body weight, the dependent variables kidney length (coefficient ± SE: 0.04 ± 0.01), kidney volume (0.16 ± 0.04), eGFR (0.05 ± 0.02) and mGFR (0.33 ± 0.04) were positively associated with 24h UER (all: p <0.01).
Conclusion: The positive associations between urinary uromodulin excretion rate, measured and estimated GFR, renal length and renal volume suggest that urinary uromodulin excretion might be a new marker of renal function and mass.

P 29

Caffeine levels are inversely associated with kalemia in women: a population based Study

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Introduction: Previous case reports have described the association between excessive caffeine consumption and hypokalemia. Population-based studies are however lacking and most studies do not measure blood caffeine levels. We examined the association of plasma caffeine levels with potassium in a population-based sample.
Methods: The Swiss Kidney Project on Genes in Hypertension is a family-based multi-centre (Lausanne, Bern, Geneva) population-based study that examines the genetic determinants of renal function and blood pressure. We measured plasma caffeine and potassium levels. Multilevel mixed-effect linear regression was used to examine the association of plasma caffeine tertiles with blood and fractional excretion of potassium, while taking familial correlations into account.
Results: The 536 men and 592 women included in this analysis had a median plasma caffeine level of 556.5 and 624.0 ng/ml, respectively, and a mean (±SD) plasma potassium level of 4.1 (0.3) mmol/l. There was an inverse association between plasma potassium and the third caffeine tertile among women (β coefficient = –0.08 mmol/l; p = 0.024), but not among men. This association was significant only for women taking the oral contraceptive pill (β coefficient = –0.29 mmol/l; p <0.001). There was a positive association between the third caffeine tertile and fractional excretion of potassium in women (β coefficient = 1.03%; p = 0.001) but not in men. There was no significant association between plasma caffeine levels and diuresis.
Conclusion: We found an inverse association between plasma potassium and caffeine levels uniquely among women, suggesting that this association may be influenced by sex hormones.

P 30

Parathyroid Hormone, Hyperparathyroidism and Chronic Kidney Disease in Primary Care

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Purpose: To investigate the levels of parathyroid hormone (PTH) and the prevalence of hyperparathyroidism (HPT) in patients with or without chronic kidney disease
(CKD) in a primary care setting.
Methods and Materials: A multicenter, cross-sectional study in seven Swiss cantons was performed. Adult patients visiting the randomly selected general practitioners during defined periods were asked to participate. Emergency patients were excluded. Demographic and social variables, clinical status and co-morbidities were reported on a questionnaire. Urine and blood samples were sent to a central laboratory for analysis. CKD was assessed by creatinine-based estimates of the glomerular filtration rate (eGFR), calculated with the CKD-EPI equation, and by albumin creatinine ratio (ACR). Hyperparathyroidism was defined as PTH ≥65 pg/ml.
Results: 1'000 patients were included. 57% were women and the mean age was 57 ± 17 years. Mean PTH was 68 ± 46 pg/ml. The prevalence of HPT was similar between genders (42.2% females, 39.7% males). Both decreasing eGFR and increasing ACR were associated with increasing PTH values and HPT prevalence (p <0.001). Overall, the prevalence of HPT was significantly higher in CKD patients, if compared with patients with normal eGFR and ACR (51.3% versus 38.1%, p <0.001).
Conclusion: These results suggest that the prevalence of elevated PTH in primary care is high, especially for CKD patients. Testing PTH in patients with reduced eGFR and/or elevated ACR might allow early detection and treatment of HPT, reducing disease progression and mortality.

P 31

Copeptin is associated with the presence of cysts and renal function in the general Population

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Introduction: Copeptin is the c-terminal part of the vasopressin (VP) precursor peptide. Recent studies have demonstrated a role of VP in polycystic kidney disease and deterioration of renal function. Our aim was to analyze the association of copeptin levels with cysts and renal function in the general population.
Method: The Swiss Kidney Project on Genes in Hypertension study included random families from the general population in Lausanne, Geneva and Bern. In each center, renal ultrasound was performed according to a standardized protocol. Fasting blood and 24h urine were collected. Renal function was assessed with 24h urinary albumin-to-creatinine ratio and glomerular filtration rate (eGFR) using CKD-EPI equation. Multilevel logistic and linear regression analyses were conducted taking into account the family effect. Results
Results: We included 411 men and 448 women in the present analysis, respectively aged 46.1 ± 17.9 and 48.2 ± 17.4 (p = 0.08). Copeptin levels were significantly higher in men than in women (median 5.3 vs 3.1 pmol/L, p <0.001). Adults with cysts (n = 102), eGFR <60 ml/min (n = 28) or albuminuria (n = 37) had also higher copeptin levels, than adults without those conditions: median 4.9 vs 3.9 pmol/L; 5.3 vs 4.0 pmol/L and 5.3 vs 4.0 pmol/L, respectively (all p <0.004). In multivariate analysis we observed associations between: copeptin levels and presence of cysts [Odds 2.0; CI 95% 1.2–3.4, p = 0.004]; copeptin and albuminuria [b coefficient 0.2; CI 95% 0.1–0.3, p = 0.001]; copeptin and eGFR [b coefficient – 3.0; CI 95% 4.7–1.3, p <0.001].
Conclusion: In a cross-sectional population–based study, we found that high copeptin levels were associated with high prevalence of renal cysts and lower renal function. These results highlight the potential role of vasopressin in the control of renal function.

P 32

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/mn 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/mn) 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/mn were subsequently reviewed by a panel of nephrologists.
Results: From May 1st up 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/mn and 196 ± 172 mmol/L respectively. One third had superimposed AKI on CKD. Etiology of AKIs was prerenal (76%), 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.

P 33

Microhematuria in ADPKD

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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 stage 1. For CKD stage 3, the hazard ratio increased to ~3.5 fold when compared to CKD1. No events were recorded for CKD 0. A model for htTKV demonstrated a 6.5% risk increase per 100 cm^3 additional volume of renal mass. The risk for patients to develop micohematuria in htTKV 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.

P 34

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, HCO_3^- ≥27 mmol/L) can be found in cystic fibrosis patients on drug treatment (especially diuretics and alkalinizing 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 >60 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 ≤2.5 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 repaired parenterally, 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.

P 35

Hyperchloremic metabolic acidosis induced by the iron chelator deferasirox (Exjade®): a case report and review of the literature

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Background: Deferasirox (Exjade®) is a new treatment of iron overload that is administered orally once-a-day, resulting in better acceptance in among patients. Deferasirox-induced renal tubular dysfunction has been reported on very rare occasions.
Case summary: A 17-year-old female adolescent with β-thalassaemia on deferasirox 30 mg/kg daily since 6 months presented with isolated hyperchloremic metabolic acidosis (bicarbonate 12.9 mmol/L, sodium 137 mmol/L, chloride 111 mmol/L, potassium 3.6 mmol). Creatinine, urea, uric acid, total calcium, inorganic phosphorous and urinalysis were normal. Acidosis resolved after withdrawing deferasirox. The Naranjo adverse drug reactions probability scale indicated that a relationship between deferasirox and hyperchloremic metabolic acidosis is likely.
Review of the literature: Eight cases of metabolic acidosis have been reported in patients treated with deferasirox. In most cases, acidosis was associated with further features of proximal renal tubular dysfunction (such as hypophosphatemia, hypokalemia, hypouricemia, glucosuria in the face of a normal blood glucose level, generalized hyperaminoaciduria and mild proteinuria). In 3 further cases signs of renal tubular dysfunction were noted that were associated with a normal acid–base balance.
Conclusion: We describe herein a case of metabolic acidosis in the setting of treatment with the deferasirox. Our case and the literature indicate a potential risk of kidney toxicity on this agent.

P 36

Severe signs of dilutional hyponatremia secondary to desmopressin treatment for nocturnal enuresis: A systematic review of the literature

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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 recognized complications of 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.

P 37

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: Fourty-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 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.

P 38

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.

P 39

Continuous subcutaneous magnesium infusion by portable pump for severe congenital hypomagnesaemia

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Background: Chronic hypomagnesaemia from renal or intestinal losses remains a therapeutic challenge, because oral supplementation is limited by diarrhea. We for the first time report continuous subcutaneous magnesium (Mg) infusion as an effective treatment option.
Case report: A 27 year old patient was referred for treatment of severe refractory hypomagnesaemia. Serum Mg levels <0.4 mmol/l with occasional epileptic fits had been present from her infancy. Stool magnesium was massively increased (1069 and 1560 mg/kg), whereas renal fractional Mg excretion was only mildly elevated (3% at 0.4 mmol/l, 7% at 0.8 mmol/l serum Mg). Despite oral Mg supplements of up to 70 mmol/d, she required almost weekly i.v. Mg infusions to keep plasma Mg ≥0.3 mmol/l, a level below which paresthesias and cramps invariably developed. Additional diagnoses included autoimmune hypothyroidism and Addison's disease.
Intervention: In February 2013, the patient was supplied with a portable insulin pump (Accu-chek spirit, Roche®), and a s.c. infusion catheter set. The 3 ml pump reservoir was filled with undiluted 50% $MgSO_4$ solution (2 mmol/ml). The pump was set at an infusion rate of 0.1 ml/h to deliver 4.8 mmol of Mg^{2+} per day. The s.c. catheter was replaced every 2 to 3 days by the patient. Serum Mg^{2+} promptly increased and over the following 6 months remained at a mean 0.52 mmol/l (± 0.06 SD) without any additional Mg supplement. Paresthesias and cramps subsided as well as diarrhea, which previously had been driven by oral Mg. Two episodes of subcutaneous infection, one with coagulase negative staphylococci, were controlled by catheter replacement and antibiotics.
Conclusion: Continuous subcutaneous magnesium infusion is a promising and effective treatment for severe resistant hypomagnesaemia.

P 40

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 poor survival.
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 osteoclastic activity and lower free fetuin-A, plasma pyrophosphate 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 lowest tertile was nearly five times the risk compared to those 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.

P 41

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 estimated 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-dehydrocorticosterone + tetrahydrocorticosterone + 5α-tetrahydrocorticosterone) / (tetrahydrocortison + tetrahydrocortisol + 5α-tetrahydrocortisol) and ratio 2 = (tetrahydro-11-dehydrocorticosterone + tetrahydrocorticosterone + 5α-tetrahydrocorticosterone) / (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.

P 42

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

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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 placental function by local aldosterone production in endothelial cells within the fetal umbilico-placental circulation.
Aim: We aimed to identify local endothelial aldosterone production.
Results: As initial readout, we incubated either HUVECs or HVSMCs with aldosterone with or without the aldosterone antagonist spironolactone. PlGF, 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 PlGF expression following treatment with spironolactone was observed, suggesting local aldosterone production. In HUVECs, we identified large amounts of CYP11B2 (aldosterone synthase) protein and aldosterone production from progesterone, DOC and corticosterone. This 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.

P 43

Another Unexpected Role of Aldosterone in Pregnancy: Placental Angiogenesis via PlGF 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 (PlGF) 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 PlGF.
We analysed TH-Aldosterone concentrations in urine (by GC-MS) and PlGF in the serum (by Elisa) of 34 pregnant women throughout pregnancy. We observed a direct linear correlation between TH-Aldosterone and PlGF. We excluded aldosterone secretion secondary to PlGF 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 stimulator forskolin, increasing amounts of aldosterone (10^{-11} to 10^{-6} M) and the competitive aldosterone receptor blocker spironolactone for 6 and 24 hrs. PlGF mRNA was stimulated upon the addition of different aldosterone concentrations in primary human and also the trophoblast cell line BeWo in combination with forskolin. PlGF 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 PlGF expression in pregnancy likely accounting for the majority of circulating PlGF. This adds a further novel protective mechanism for aldosterone in pregnancy, thus responding via this steroid hormone to unfavourable environmental conditions.

P 44

Normotensive Blood Pressure in Pregnancy – The Role of Salt and Aldosterone

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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 phenotype in pregnancy.
We compared normotensive pregnant women (n = 31) throughout pregnancy to young healthy female individuals (n = 31–62) and performed salt sensitivity testing within the first trimester. Suppression of urinary tetrahydroaldosterone levels by salt intake as measured by gas chromatography-mass spectrometry and urinary Na^+ excretion corrected for creatinine, respectively, was shifted towards a higher salt intake in pregnancy ($p < 0.0001$). In pregnancy, neither high urinary tetrahydroaldosterone nor Na^+ excretion were correlated with higher blood pressure. In contrast, in non-pregnant women systolic blood pressure rose with aldosterone ($p < 0.05$). Testing the impact of salt on blood pressure, we performed salt sensitivity testing in a final cohort of 19 pregnant and 24 non-pregnant women. Upon salt loading, 24-h mean arterial pressure rose by 3.6 ± 1.5 and dropped by –2.8 ± 1.5 mm Hg favoring pregnant women ($p < 0.01$; $\chi^2 = 6.04$, $p < 0.02$).
Our data suggest first that salt responsiveness of aldosterone is alleviated in conditions of pregnancy without causing aldosterone-induced hypertension. Second, salt appears to aid blood pressure lowering in pregnancy for reasons incompletely elucidated, yet involving renin suppression and potentially placental sensing mechanisms. Further research should identify susceptible individuals and clarify effector mechanisms.

Poster presentations – Dialysis

P 45

Outcome of dialysis patients above and below seventy years 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 type 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.

P 46

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, Interlaken, 2000 IU/tbl) 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 ± 16.1 vs 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 calcitirol – 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.

P 47

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

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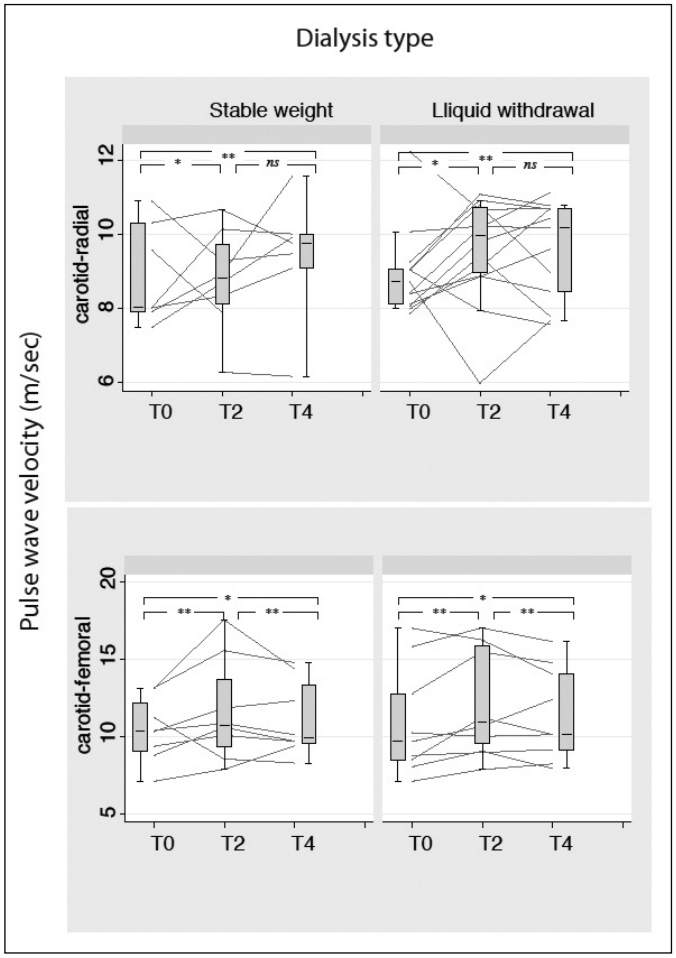
Introduction: Arteries of end-stage renal disease patients are characterized by accelerated atherosclerosis and chronically progressive arterial stiffening. The acute effects of hemodialysis sessions on arterial properties have been less intensively studied, with contradictory results, possibly due to 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: A total of 13 hemodialysis patients undergoing ultrafiltration (UF) and 8 patients dialyzed at stable body weight (SW) underwent applanation tonometry using the Complior 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 peripherical 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 ($p_{interaction} = 0.97$), 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.



P 48

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

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Background: High- and low-flux dialysis membranes could 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 m^2 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. Kt/V 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 s*mm Hg/ml; 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.

P 49

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

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The TRANSIT observational multicenter survey collected data from 172 Swiss hemodialysis patients treated with cinacalcet (CIN) 2009–2013 for secondary hyperparathyroidism (sHPT) to evaluate the attainment of K/DOQI and KDIGO treatment goals and the role of concomitant active vitamin D therapy. We here report data from 113 patients with 12 months' followup.
Methods: Monthly data on corrected serum calcium (cCa), phosphate (Pi), iPTH, and comedication were collected from 6 months prior to CIN therapy to 12 months after CIN start. Active vitamin D in addition to CIN treatment was categorized as either high dose (HiD: calcitriol >0.75 µg/d or paricalcitol >6 µg/d), LowD or NoD (if only CIN was given).
Results: In 79 (70%) of the 113 patients, treatment in the 6 months before CIN included active Vitamin D. 12 months after CIN therapy start, 34 patients received HighD, 28 LowD and 31 NoD in addition to cinacalcet. Treatment goal compliance is shown below:

	K/DOQI target			KDIGO target		
	iPTH 16.5–33.0 pmol/l	cCa 2.10–2.37 mmol/l	Pi 1.13–1.78 mmol/l	iPTH 13.7–61.6 pmol/l	cCa 2.10–2.55 mmol/l	Pi 0.81–1.45 mmol/l
Baseline before CIN	6%	49%	50%	43%	78%	20%
12 months	27%	45%	59%	62%	60%	40%

Reasons for not reaching calcium targets were hypocalcemia (<2.1 mmol/l in 26%) as well as hypercalcemia (29% >2.37 mmol/l, 15% >2.55 mmol/l). The iPTH response did not appear related to active Vitamin D dose (median decrease –55% with HiD, –61% with LowD, –50% with NoD). The median decrease of cCa was somewhat less with HiD (–4%) than with LowD (–19%) or NoD (–16%).

Summary: TRANSIT confirms in a real-life setting, that sHPT treatment with cincalcet helps to reach iPTH and Pi targets. The impact of Cinacalcet initiation on calcium target achievement remains to be further evaluated.

Poster presentations – Experimental nephrology

P 50

Sodium thiosulfate may prevent vascular calcifications via its metabolite H_2S

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Background: Vascular calcification and more specially the calcification of vascular smooth muscle cells (VSMC) are a common problem in chronic kidney disease (CKD). Sodium thiosulfate (STS, Na2S2O3) prevents vascular calcifications in uremic rats. Calciprotein particles (CPP) are calcium phosphate containing nano-aggregates which can be found in the blood of CKD patients. The aims of this research project are to (i) establish a model of calcification of VSMC *in vitro* using CPP and (ii) to elucidate how STS may inhibit vascular calcification.
Methods: Amorphous primary and crystalline secondary CPP were generated using calcification medium incubated at 37°C for 2 hours and 7 days, respectively. CPP were characterized by measuring absorbance at 570 nm, measuring calcium and phosphate concentrations and by transmission electron microscopy (TEM). VSMC were cultured in calcification medium/CPP-enriched media. Mineralization was assessed by quantification 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. Exposer of calcifying VSMC to STS led to on 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.

P 51

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.
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 confirmed.

P 52

Beta-oxidation affects the susceptibility of podocytes to palmitic acid: Critical role of Acetyl-CoA Carboxylase 1 and 2

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Introduction: Type 2 diabetes (T2D) is characterized by dyslipidemia with elevated free fatty acids (FFAs). FFAs and renal FFA-oxidation (FAO) potentially play a direct role in diabetic nephropathy (DN), and a SNP in acetyl-CoA carboxylase (ACC) 2 is associated with proteinuria in T2D. SNP results in higher expression of ACC2 which likely inhibits FAO by producing higher malonyl-CoA, an inhibitor of carnitine palmitoyltransferase I (CPT1). Here, we studied FAO, and role of ACCs in palmitic acid induced cytotoxicity.
Methods: Conditionally immortalized murine podocytes differentiated for at least 11 days were used. Aicar (AMPK agonist) and etomoxir (CPT1 inhibitor) were employed to alter FAO. 3H palmitic acid was used to determine FAO. ACC 1 and 2 were silenced using lentiviral system.
Results: Aicar decreased palmitic acid induced apoptosis and necrosis by 50.5 ± 1.5% ($p < 0.01$) and 42.5 ± 6.1% ($p < 0.05$), whereas etomoxir exacerbated them significantly. Aicar phosphorylated AMPK and ACC. Aicar increased oxidation of palmitic acid by 146.6 ± 22.0% ($p < 0.05$) and co-treatment with etomoxir reversed this effect. Only knocking down of both ACC 1 and 2 reduced palmitic acid induced apoptosis 59.6 ± 4.5% ($p < 0.01$) and necrosis 64.4 ± 6.4% ($p < 0.01$).
Conclusions: Regulation of FAO in podocytes profoundly affects their susceptibility to palmitic acid toxicity. Our data may explain the risk for proteinuria in T2D patients with SNP in ACC2 as reported in previous studies. AMPK-ACC-CPT1 pathway is a potential target to prevent and treat DN.

P 53

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 untreate uremic controls, as well as APO- and TAU-treated animals. Like in the aorta, calcium conten 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.

P 54

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

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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 what 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.

P 55

Physiological Role of the Mediator of ErbB2 Induced Cell Motility (Memo) in Mice

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The 33kDa mediator of ErbB2 induced cell motility (Memo) protein interacts with fibroblast growth factor (FGF), insulin receptor substrate protein 1, and estrogen signaling, but its physiological role is still poorly understood. Inducible Memo 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 Memo is expressed in the bone and required for the bone’s FGF receptor signaling and the regulation of FGF-23 secretion.
Tissues of C57/BL6 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-Memo antibodies respectively.
Memo 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. Memo protein expression was higher in bone fractions than in the kidney (3 independent experiments) and other organs. Over time, Memo 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. Memo is expressed widely, such as in the three main sites of calcium and phosphate regulation, the bone, intestine and kidney. The peak of bone Memo mRNA at 4 weeks, which correlates with maximal growth in mice suggests that Memo 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 Memo KO mouse model.

Poster presentations – Renal pathology

P 56

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 arteriolohyalinosis, intimal 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 3p21.1-3p21.3 such as cerebroretinal vasculopathy (CRV), hereditary endotheliopathy with retinopathy, nephropathy and stroke (HERNS) and hereditary vascular retinopathy (HVR). Similarities and differences of these entities will be discussed.
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.

P 57

Fibrosis of Solid Organs: Towards a Common Classifier across Species

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Background: We described a transcriptomic classifier of metzincins and related genes (MARGS) discriminating renal allograft biopsies with/without fibrosis and extended analyses to non-transplant solid organs (AJT,2009; Virchows 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 = 76) 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 level 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 gene expression data into non-fibrosis (n = 4) and fibrosis (n = 16). Immunofluorescence confirmed up regulation of MMP-2 and CD44 in fibrosis. Analyses of miRNA targeting MARGS are in progress, which should provide insight into gene regulation networks important for 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.

P 58

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 (EVN; 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 EVN and – after exclusion of amyloidosis – in ZRH by LM, electron microscopy (EM) and immunohistochemistry (last 79). Biopsies from ZRH were evaluated by LM, EM and immunofluorescence.
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 EVN (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 nephro-pathy 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.

Poster presentations – NCCR Kidney.CH

P 59

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)-β/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 analyses coupled with histological investigation are suggestive of possible roles of Fxr in this model of renal disease. The results shed a light on unraveling complex mechanisms contributing to high-fat diet induced renal damage.

P 60

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 transcellular 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 claudin-4 and 8 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 addressing 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.

P 61

Furosemide stimulation of parathyroid hormone in humans: role of the calcium-sensing receptor and renin-angiotensin system

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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-naive 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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P 62

V-ATPase B1 subunit polymorphism p.E161K affects urinary acidification in vivo

Nasser Dhayat, Andreas Pasch, Daniel Fuster

The V-ATPase proton pump on the luminal membrane of α–intercalated cells is critical for urinary acidification. The V-ATPase consists of two multi-subunit domains, the V_0 and V_1 domain. The soluble cytosolic 640 kDa V_1 domain is composed of subunits A-H in a $A_3B_3C_1D_1E_1F_1G_2H_1$ stoichiometry. In humans, there are two different isoforms of the B subunit in the V_1 domain, of which B2 is ubiquitous whereas B1 is restricted to specialized epithelia of the inner ear, epididymidis and the distal renal tubule. Mutations in the B1 subunit gene *ATP6V1B1* cause *autosomal-recessive* distal renal tubular acidosis. We previously identified a polymorphism in the human V-ATPase B1 subunit (p.E161K) that greatly diminished pump function *in vitro* (Fuster, Moe et al., *Kidney Int* 2008). To study the impact of the p.E161K polymorphism on acidification in humans *in vivo*, we conducted a study in our renal stone patient registry. Patients heterozygous for the p.E161K polymorphism (n = 19) tended to be younger at presentation (35 vs 42 years) and had higher 24 hr urinary pH (6.48 vs 6.06; $p = 0.02$) than patients carrying two wild-type alleles (n = 249). Blood pH, pCO_2 and HCO_3^- and 24 hr sulphate excretion (measure of protein intake) were not different between the two groups of patients. Ammonium chloride loading tests revealed a mild urinary acidification deficit in heterozygous (n = 12; mean nadir urinary pH 5.16) carriers when compared to subjects carrying two wild-type alleles (n = 32; mean nadir urinary pH 4.88) but the difference did not reach significance ($p = 0.07$). A single subject homozygous for the polymorphism identified so far exhibited a pathological urinary acidification test compatible with incomplete distal tubular acidosis (nadir urinary pH 5.35). Thus, our data reveal a mild urinary acidification deficit in p.E161K heterozygotes and incomplete distal tubular acidosis in p.E161K homozygotes. Clearly, however, a greater numbers of subjects is needed to definitively clarify the role of this polymorphism in urinary acidification in man.

P 63

Flow-mediated regulation of sodium transport in the collecting duct

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Sodium (Na) transport in renal tubules is tightly controlled and plays a central role in homeostasis of the body extracellular fluid volume. In addition to the classical neuro-endocrine regulatory inputs (incl. RAA system), other local factors such as tubular luminal flow might participate to Na homeostasis. We designed an *in vitro* experimental setting to explore the effect of apical flow on a cellular model of collecting duct (CD) using the well-described mouse CD cell line $mCCD_{cl1}$ grown on polycarbonate filters. Directional flow was generated using an orbital shaker delivering a shear stress of 2 dyne/cm^2 mimicking physiological luminal flow. We observed a delayed and sustained 40% decrease of the amiloride-sensitive Na current in cells subjected to flow. This was correlated with a significant decrease of ENaC subunits and SGK1 mRNA expression. The flow-mediated Na transport reduction did not require a functional primary cilium as demonstrated using mCCD cells silenced for PKD1 or KIF3A. In contrast, flow induced a cAMP-independent PKA activation and PKA inhibition partially preventing the flow-mediated decrease of Na transport *in vitro* as well as the downregulation of ENaC subunits mRNA expression. In addition, PKA activation was associated with a flow-mediated increase of endothelin-1 transcriptional expression. These *in vitro* observations are in line with the physiological adaptation after unilateral uninephrectomy observed in rodents where an increase in tubular fluid delivery is observed together with an increased CD fractional excretion of sodium. We are currently investigating whether shear stress per se is involved in this adaptive mechanism as well as confirming the involvement of endothelin-1 in flow-mediated Na transport regulation.

P 64

Impact of uninephrectomy on body L-arginine homeostasis and blood pressure control in mice

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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. C57B/6 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 suggested 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 complementation may compensate for a potential change in L-arginine production post-surgery.

P 65

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 celltype-specific response to hypoxia and the relevance of given HIFs we investigated gene expression profile of HK-2 cells and podocytes with stable HIF1α and/or HIF2α suppression under hypoxic conditions. In HK-2 cells microarray analysis revealed 163 (86% HIF1α and/or HIF2α dependent) significantly up- and 31 (81%) downregulated hypoxia target genes. In podocytes, 416 (47% HIF1α and/or HIF2α dependent) genes were significantly up- and 318 (95%) 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 celltype-specific dysregulation of hypoxia-associated gene transcripts.

P 66

Very early exposure of fetal kidneys to chronic hypoxia triggers upregulation of genes involved in glucose and fatty acid metabolism

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Chronic kidney diseases (CKD) are a growing public health problem, notably due to aging of the population and higher prevalence of the metabolic syndrome. Intrauterine Growth Restriction (IUGR) due to inadequate supply of oxygen and/or nutrients during pregnancy was proposed as an early event in life contributing to adult hypertension, insulin resistance, cardiovascular and renal diseases. However, studies of IUGR are scarce and the molecular actors responsible for a deficient nephrogenesis need to be identified.
Here we analyzed the impact of hypoxia on kidney development using a mouse model of chronic fetal hypoxia. Pregnant mice exposed to hypoxia (9.5% *vs.* 21% O_2) at day E11.5 of gestation (start of branching morphogenesis) until birth (E18.5) had decreased food intake with no reduction in litter sizes. Pups from hypoxic dams showed a significantly lower birth weight compared to normoxic or caloric control pups, thus fulfilling the criteria of IUGR. Furthermore morphometric analysis demonstrated a significant decrease in glomerular numbers in IUGR pups. Microarray analysis of E18.5 kidneys showed an upregulation of genes related to the HIF pathway, such as Bhlhe40, Slc2a1, Egln3. Importantly these genes have also been found to be upregulated in IUGR human babies and Egln3 is involved in placental regulation of HIF1α. Moreover BNIP3 – a gene involved in cell survival under energy deprivation – was also upregulated. Altogether these findings demonstrate modulation of both glucose and fatty acid metabolism correlating with IUGR development. Further analyses are ongoing to determine their expression site within the newborn's kidney.

P 67

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

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IgA nephropathy (IgAN) is the most common cause of primary glomerulonephritis 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 mm^2) were collected by laser microdissection (LMD) from tissue sections with 10 µm thickness. Peptides were extracted from the pretreated glomerular sections using OSDD – 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 glomerulus data, C7, C3, IgA and other 15 proteins significantly increased in IgAN glomerulus. A total of 7'837 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.

P 68

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 bladder carcinomas in rats. We recently identified cyclamate as the potential cause 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 17 ± 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.

P 69

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 PO_2 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 PO_2 measurements. Here we propose a convection-dominated O_2 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.

P 70

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 turn-over.
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.

The numbers refer to the pages of this supplement.