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ABSTRACTS OF THE CANCELLED 52ND ANNUAL MEETING OF THE SWISS SOCIETY OF NEPHROLOGY (SGN-SSN)

DECEMBER 2020

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ORAL COMMUNICATIONS – BASIC SCIENCE / GENETICS / EXPERIMENTAL NEPHROLOGY

OC 1

Aldosterone signaling modulates paracellular sodium permeability in renal collecting duct by regulating the over-expression of claudin-8

Ali Sassi 1, Yubao Wang 1, Alexandra Chassot 1, Isabelle Monnay 1, Edith Hummler 2, Eric Feraille 1

1. Department of Cellular Physiology and Metabolism, University of Geneva, CMU, Geneva, Switzerland , 2. Department of Biomedical Sciences, University of Lausanne, Lausanne, Switzerland

Background

Water and solute transport across epithelia can occur via the transcellular or paracellular pathways. The aldosterone-sensitive renal collecting duct (CD) is the place of a precise and tight regulation of sodium and is mainly regulated by aldosterone. Tight junctions play a key role in mediating paracellular ion reabsorption in the kidney. Claudin-8 is one of the main tight junctions proteins expressed in the CD. Coupling between transcellular sodium reabsorption and paracellular permeability may prevent the back-flux of reabsorbed solutes and may promote paracellular Cl- reabsorption. We hypothesize that aldosterone controls both transcellular and paracellular permeability in a coordinated manner.

Methods

Male mice were fed for 7 days with either low (0.01% wt/wt), normal (0.18% wt/wt) or high sodium (1.25% wt/wt). One group of mice fed a low sodium diet received 0.35 mg/100 g body wt/day of spironolactone for 7 days. We also used mice with kidney tubule-specific MR deletion and cultured mCCD cells to elucidate the mechanism of action of aldosterone on claudin-8 expression.

Results

We show here that low salt diet stimulates aldosterone secretion and increases claudin-8 abundance in mouse kidney. Reciprocally, claudin-8 abundance is decreased in kidneys of the mice fed with a high salt diet that blunted aldosterone secretion. In agreement, mice treated with spironolactone, a mineralocorticoid receptor (MR) antagonist, and mice with kidney tubule-specific MR deletion displayed a strong down-regulation of claudin-8. In cultured CD principal cells, aldosterone increased claudin-8 and enhanced transepithelial resistance but did not alter ZO-1 expression. Inhibition of the GSK3 pathway decreased claudin-8 expression and prevented the effect of stimulated transcellular Na+ transport.

Conclusions

Our results show that aldosterone modulates the expression of claudin-8 via GSK3 signaling pathway and reveal a coupling between transcellular and paracellular sodium transport that may prevent the back-flux of reabsorbed water and solutes.

OC 2

Dietary magnesium counteracts oxidative and ER stress in mouse models of CKD in a gender-specific manner (NCCR project)

Stefan Rudloff 1, Deborah Bächler 1, Delphine Lambert 1, Olivier Devuyst 2, Uyen Huynh-Do 1

1. Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern and Department for BioMedical Research, University of Bern, Bern, Switzerland 2. University Hospital of Zurich, Zurich, Switzerland

Background

Epidemiological studies have shown that low serum magnesium (Mg) levels are associated with an increased risk for chronic kidney disease (CKD). However, the molecular mechanisms involved in the putative protective effect of Mg on CKD remain unclear. We used a surgical and a genetic mouse model to address the question how Mg affects renal fibrosis and the progression of CKD in both sexes.

Methods

For surgical induction of CKD, we performed unilateral ureteric obstruction (UUO) in C57BL/6J mice. The genetic mouse model makes use of a mutation in uromodulin (Umod) that prohibits its proper processing in the ER. Mice either received a control diet (0.2% Mg) or a Mg-enriched diet containing 0.8% Mg. To study kidney function, the glomerular filtration (GFR) was assessed in Umod mice. Blood, urine and kidney samples were assessed for markers of renal dysfunction, oxidative and ER stress using standard molecular methods, including RT-qPCR, histology, enzymatic assays and ELISA.

Results

Dietary Mg supplementation led to an increase in serum Mg levels and diminished the expression of fibrotic markers in the kidneys of both experimental models. Furthermore, the degree of DNA and lipid oxidation was reduced in animals receiving the Mg enriched diet. Functionally, Umod mice of both sexes showed a diminished GFR at 11 weeks that was rescued by Mg, yet the underlying mechanism showed gender-specific differences: Mg supplementation in Umod males reduced ER stress downstream of Atf4, whereas in Umod females the Atf6-mediated branch of ER stress was affected.

Conclusions

Mg supplementation counteracts renal fibrosis and loss of kidney function in 2 mouse models of CKD by reducing oxidative and ER stress. These findings suggest that Mg provides an efficient and affordable dietary treatment option to slow the progression of CKD in patients. However, close attention should be paid to sexspecific differences in the response to Mg supplementation.

OC 3

Changes in NAD and lipid metabolism drive acidosis induced acute kidney injury *

Milica Bugarski 1, Susan Ghazi 1, Marcello Polesel 1, Joana Delgado Martins 2, Andrew Hall 3

1. Institute of Anatomy, University of Zurich, Zurich, Switzerland 2. Center for Microscopy and Image Analysis, University of Zurich, Zurich, Switzerland 3. Institute of Anatomy, University of Zurich; University Hospital of Zurich, Zurich, Switzerland

Background

The kidney has an important role in maintaining normal blood pH. Mitochondria in the proximal tubule (PT) produce ammonia and bicarbonate from glutamine, and during metabolic acidosis (MA) this pathway is upregulated. MA is frequently associated with acute kidney injury (AKI); however, to what extent the former causes the latter, and thus whether MA should be treated, was unclear.

Methods

Tubular cell structure and function in mouse kidney cortex was assessed with live imaging of mitochondrial and transport function, oxygen consumption rate (OCR) measurements in isolated tubules, histological analysis and electron microscopy in fixed tissue, and urinary biomarkers. Acute MA was induced by gavage with ammonium chloride.

Results

MA induces an acute change in NAD redox state (towards oxidation) in PT mitochondria, without changing mitochondrial energization state. This is associated with a switch towards complex I activity and decreased maximal OCR, and a major alteration in fatty acid metabolism, resulting in marked lipid accumulation in PTs and the formation of large multi-lamellar bodies. These changes in turn lead to acute tubular damage and a severe defect in solute uptake. Increasing blood pH with intravenous bicarbonate substantially improves tubular function, while pre-injection with the NAD precursor nicotinamide is highly protective.

Conclusions

MA induces AKI via changes in PT NAD and lipid metabolism, which can be reversed or prevented by treatment strategies that are viable in humans. These findings might also help to explain why MA accelerates decline in function in chronic kidney disease.

* *Student paper*

OC 4

High-content imaging of human-derived kidney tubular cell function reveals a mechanism for Tenofovir toxicity (NCCR project) *

Adam Pearson 1, Dominik Hänni 2, Andrew Hall 3

1. Institute of Anatomy, University of Zurich, Zurich, Switzerland 2. University of Zurich, Center for Microscopy and Image Analysis; Institute of Anatomy, University of Zurich, Zurich, Switzerland 3. Institute of Anatomy, University of Zurich; University Hospital of Zurich, Zurich, Switzerland

Background

Globally, millions of people live with HIV and hepatitis B (HBV). Toxicity from antiretroviral drugs is a major cause of kidney disease in these individuals. Tenofovir disoproxil fumarate (TDF) is a first line therapy for HIV and HBV. TDF induces functional proximal tubule (PT) defects for

reasons that are unknown, partly due to a lack of appropriate experimental models. Clinically, TDF toxicity is characterized by two major phenotypes: isolated defects in PT solute transport; and severe damage associated with mitochondrial morphology and cristae abnormalities. The aim of our study was to establish representative *in vitro* models of TDF toxicity, to investigate the underlying mechanisms.

Methods

Experiments were performed on monolayers of differentiated human-derived PT cells (RPTEC/TERT1). A highcontent image analysis pipeline was established, using automated microscopy and machine learning, to quantify transport function, using dome formation as a readout. Metabolism was evaluated by antibody staining for mitochondria and autophagy.

Results

We screened numerous treatment regimens and generated phenotypes matching those observed in patients, including transport inhibition and mitochondrial abnormalities. Multi-modal analysis of these models – including oxygen consumption assays, metabolomics and RNA sequencing – revealed specific decreases in ATP-linked respiration, cellular ATP, and expression levels of genes related to complex V (ATP synthase) function and cristae formation. Metabolomic analysis confirmed TDF was converted within cells to the active antiviral metabolite Tenofovir diphosphate (TFVpp), a structural analogue of ATP. Using an*in vitro* assay of complex V activity, we observed a dose dependent inhibition with TFVpp.

Conclusions

In summary, we have developed a high-content image analysis pipeline of PT cell function to generate realistic *in vitro* models of TDF toxicity. Multi-parametric characterization of these revealed a clear phenotype consistent with complex V inhibition, which likely explains toxicity observed in patients, since PT solute transport is heavily dependent on aerobic respiration.

* *Student paper*

OC 5

Administration of fetuin-A attenuates fibrotic remodeling and improves renal function in mouse models of pre- and postrenal injury (NCCR project)

Ricardo Villa-Bellosta [1], Stefan Rudloff [1], Uyen Huynh-Do [1]

1. *Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern and Department for BioMedical Research, University of Bern, Bern, Switzerland*

Background

Ischemia-reperfusion is a leading cause of acute kidney injury (AKI) in hospitalized patients and contributes to increased morbidity and mortality. Fetuin-A is a circulatory, liver-derived glycoprotein that beyond its role as a systemic calcification inhibitor was recently shown to counteract hypoxic tissue damage in the fetal kidney. Here we addressed the question if fetuin-A administration improves renal function and tissue recovery in 2 mouse models of kidney injury.

Methods

For pre-renal injury, we performed ischemia reperfusion injury (IRI) in 10-12 weeks old C57BL/6J mice (ischemia time 30 min), for post-renal injury unilateral ureteric obstruction (UUO) was done. Mice were either treated with different dosages of fetuin-A or saline. Glomerular filtration (GFR) was assessed in bilateral IRI mice. Blood, urine and kidney samples were analyzed for markers of renal dysfunction using standard molecular methods, including RT-qPCR, histology and ELISA.

Results

Experimental IRI led to a drop in the hepatic expression of fetuin-A, whereas the expression of TNFa and IL6 were increased in liver, kidney and plasma samples. Fetuin-A treatment not only diminished these inflammatory markers, but also attenuated the expression of several fibrotic markers (Col1a1, Col3a1, Col6a1, Acta2, Fn1 and Vim) in UUO and IRI injured kidneys. Consistently, renal function was improved in treated mice compared to untreated mice.

Conclusions

A wide range of biological functions have been proposed for fetuin-A based on its structural similarities to other proteins or physical interactions with biogenic molecules. We have shown here that fetuin-A administration has anti-inflammatory, anti-fibrotic and anti-calcifying properties in 2 mouse models of renal injury. Based on these findings, fetuin-A administration could be used as a new therapeutic approach to improve renal function and mitigate fibrotic remodeling after ischemic insults.

OC 6

Chronic kidney disease impairs glucose production through gluconeogenesis downregulation (NCCR project)

Thomas Verissimo [1], Anna Faivre [1], Carolyn Heckenmeyer [1], Marylise Fernandez [1], Pietro Cippà [2], David Legouis [3], Sophie De Seigneux [4]

1. *Laboratory of Nephrology, Department of Medicine and Cell Physiology, University Hospital and University of Geneva, Geneva, Switzerland* , ***2.*** *Division of Nephrology, Ente Ospedaliero Cantonale, Lugano, Switzerland* , ***3.*** *Laboratory of Nephrology, Department of Medicine and Cell Physiology, University Hospital and University of Geneva, Geneva, Switzerland Division of Intensive Care, University Hospital of Geneva, Geneva, Switzerland* , ***4.*** *Laboratory of Nephrology, Department of Medicine and Cell Physiology, University Hospital and University of Geneva, Geneva, Switzerland Service of Nephrology, Department of Internal Medicine Specialties, University Hospital of Geneva, Geneva, Switzerland*

Background

Chronic kidney disease (CKD) is defined as an alteration of kidney structure or function lasting for more than three months. Alterations of kidney metabolism are emerging as new players in the pathophysiology of CKD, contributing to renal prognosis. The aim of our study is to better characterize the modulation of gluconeogenesis in and to better define whether the regulations we observe may play a role in the progression of renal disease.

Methods

We used different CKD mice models, a proteinuric (POD-ATTAC) and a non-proteinuric (UUO) models, to characterize the change in gluconeogenesis. We measured GFR with sinistrin-FITC clearance, gluconeogenesis renal enzymes activities, proteins and mRNA expressions in the cortical area. We also used a biobank of renal biopsies in native and allograft patients, to quantify mRNA expression of gluconeogenic enzymes in humans. We finally performed a retrospective cohort study involving patients admitted to the intensive care unit of our hospital.

Results

In human renal biopsies biobank and in our mice models, we observed an alteration of gluconeogenic pathway in CKD that was stage dependent. More precisely, we observed that gluconeogenesis enzymes (FBP1, PCK1 and G6PC) were downregulated at the mRNA, protein and activities levels and these downregulations were correlated with GFR. We further showed using a lactate tolerance test that glucose production from lactate was impaired during experimental CKD. In human biopsies, we showed that expression of PCK1 and FBP1 was predictive of fibrosis evolution. Finally, we showed that CKD was associated to metabolic alterations in patients admitted in the intensive care unit, that were predictive of a higher mortality.

Conclusions

In our study, we showed that renal gluconeogenesis is negatively regulated in CKD. We further showed that this downregulation is associated with kidney alteration through low GFR rate, long term fibrosis and may contribute to alter the prognosis of CKD patients.

ORAL COMMUNICATIONS – TRANSPLANTATION

OC 7

Therapeutic consequences of screening for de novo donor-specific HLA antibodies after kidney transplantation

Hasret Cun 1, Gideon Hönger 1, Marc Kleiser 1, Patrizia Amico 2, Caroline Wehmeier 1, Juerg Steiger 2, *Michael Dickenmann 3,* *Stefan Schaub 3*

***1.** Universitätsspital Basel, Basel, Switzerland **2.** Universitätsspital Basel, Transplantationsimmunologie und Nephrologie, Basel, Switzerland **3.** Clinic for Nephrology and Transplantation Immunology University Hospital Basel*

Background

Screening for de novo donor-specific HLA antibodies (DSA) after kidney transplantation is widely recommended, but its diagnostic and therapeutic consequences are largely unexplored. Therefore, the aim of this single-center, cross-sectional study was to investigate the frequency of therapeutic interventions triggered by de novo DSA screening.

Methods

We included 464 patients having pre-transplant testing by single antigen beads (cutoff MFI>500). Screening for de novo DSA was performed at annual visits after a median of 5 years post-transplant (range 1 to 19 years) by the same method and MFI cutoff. Diagnostic and therapeutic interventions were extracted from patient charts.

Results

Overall, de novo DSA were detected in 55/464 patients (11.9%) with a stepwise increase of the prevalence from 4.9% at one year post-transplant to 18.9% at >10 years post-transplant. Subsequent allograft biopsies were performed in 24/55 patients (44%). The main reasons to omit biopsies were good/stable allograft function and anticipated lack of clinical consequences (e.g. relevant comorbidities). Rejection processes were detected in 16/24 biopsies (67%). Therapeutic interventions were made in 18/464 screened patients (3.9%) with a significantly higher rate in the youngest quartile of patients (≤48 years; 7.9%) compared to the middle 50% (49-67 years; 3%) and the oldest quartile (≥68 years; 1.7%) ($p = 0.03$).

Conclusions

Our study suggests that the frequency of therapeutic interventions triggered by de novo DSA screening after kidney transplantation is overall low, but significantly higher in younger patients, arguing for an personalized, age-adapted de novo DSA screening strategy.

OC 8

Outcome of combined DSA-positive and AB0-incompatible living donor kidney transplantation *

Louis Aebischer 1, Stefan Schaub 2, Patrizia Amico 3, Juerg Steiger 3, Michael Dickenmann 1

***1.** University Hospital Basel, Clinic for Transplantation Immunology and Nephrology, Basel, Switzerland , **2.** Clinic for Nephrology and Transplantation Immunology University Hospital Basel, Basel, Switzerland **3.** Universitätsspital Basel, Transplantationsimmunologie und Nephrologie, Basel, Switzerland*

Background

While the knowledge on transplantation across blood group barriers (ABOi) and against donor-specific antibodies (DSA) is steadily growing, the current experience in kidney transplantation overcoming both risks is still scarce. This report compares the outcome of ABOi with (ABOi+DSA) or without (ABOi-DSA) additional HLA-DSA.

Methods

All ABOi at the university hospital Basel from 2009 to 2017 were investigated. ABOi-DSA patients were treated with Rituximab, selective blood group antibody immunoadsorption, Basiliximab induction, Tacrolimus, Mycophenolate-Mofetil, and prednisone according to the Swiss ABOi protocol. ABOi+DSA recipients received the same treatment, except induction with ATG/IVIG instead of Basiliximab, and plasmapheresis in case of highlevel circulating DSA instead of selective blood group antibody immunoadsorption. Demographic and outcome data of ABOi-DSA and ABOi+DSA recipients were compared.

Results

43 ABOi-DSA and 8 ABOi+DSA living donor kidney transplantations were performed in the defined interval. Median follow up was 1096 (37-2612) days in the ABOi-DSA, and 1525 (372-3286) in the ABO+DSA group. More female recipients (26% vs 75%), and more re-transplants (9% vs 25%) were observed in the ABOi+DSA group, otherwise the two groups were similar regarding demographic factors. Patient survival (98% vs 100%), graft survival (88% vs 100%), rejection-free survival (30% vs 50%), type of rejection, time to first rejection, eGFR after one and 5 years (55 vs 49 ml/min/1.73 m^2), number of hospital days 1st year (12 vs 11 days), and number of patients with infections requiring hospitalization (9% vs 13%) were similar between the two groups. Also IgM and IgG blood group antibody titers before treatment and after one year were not different.

Conclusions

Living donor kidney transplantation across blood group barriers and against donor-specific antibodies seems to have a similar favorable outcome as ABO incompatible kidney transplantation without the additional risk of preexisting DSA and might therefore be an option in highly selective cases.

** Student paper*

Table 1: Baseline characteristics

	AB0 n=43	AB0 + DSA n=8
Donor		
• Age in years (median, range)	51 (26 - 63)	60 (43 - 75)
• Male donor, n (%)	30 (70%)	5 (63%)
• Blood group, n (%)		
○ A	29 (67%)	4 (50%)
○ B	6 (14%)	3 (38%)
○ AB	8 (19%)	1 (13%)
Recipient		
• Age in years (median, range)	53 (21 - 68)	45 (21 - 63)
• Male, n (%)	32 (74%)	2 (25%)
• Blood group matching, n (%)		
○ A to B	6 (14%)	0
○ A to O	23 (53%)	4 (50%)
○ B to A	5 (12%)	1 (13%)
○ B to O	1 (2%)	2 (25%)
○ AB to O	2 (5%)	0
○ AB to A	4 (9%)	0
○ AB to B	2 (5%)	1 (13%)
• Median blood group antibody titer against donor blood group before treatment (median, range):		
○ IgM	1:8 (1:2-1:64)	1:32 (1:4-1:32)
○ IgG	1:8 (0-1:512)	1:32 (0-1:512)
• Re-transplant, n (%)	4 (9%)	2 (25%)
• Total HLA mismatch (A,B,DR,DQ)	4 (1 - 7)	5 (1 - 8)
• Median number of DSA (n, range)	0	1 (1-2)
• Median number of IA or PEX	4 (0 - 10)	5 (0 - 9)
• Median cold ischemia time (min)	106 (23 - 562)	86 (60 - 185)

IA: Immunoadsorption treatment before transplantation;
DSA: donor specific antibodies
PEX: plasma exchange

Table 2: Outcome until end of follow up

	ABOi n=43	ABOi + DSA n=8
Median follow up in days (median, range)	1096 (37-2612)	1525 (372-328)
Patient survival (%)	98%	100%
Graft survival (%)	88%	100%
Rejection free survival (%) (Clinical and subclinical rejection)	30%	50%
Rejection		
• Any rejection	70% (n=30)	50% (n=4)
• Subclinical rejection	43% (13/30)	50% (2/4)
• ABM rejection (n/n)	93% (28/30)	100% (4/4)
• Median time to first rejection in days	171 (0-3184)	269 (15-2071)
Median GFR ml/min (median, range; n):		
• 1 month	52 (12-124; 42)	58 (26-119; 8)
• 6 months	51 (19-109; 39)	60 (30-111; 8)
• 1 year	55 (18-118; 40)	57 (48-111; 7)
• 5 years	55 (20-103;18)	49 (23-91; 5)
Median number of hospital days 1st year[1]	12 (7-89)	11 (8-44)
• Hospital stay due to infection (n %)	4 (9%)	1 (13%)
Median blood group antibody titer against donor blood group after one year (median, range; n):		
• IgM	1:2 (0-1:16; 35)	1:8 (0-1:16; 8)
• IgG	1:2 (0-1:128; 35)	1:4 (0-1:64; 8)

ABM: antibody mediated

1: including stay for transplantation

OC 9

Outcome of Kidney Transplantation from Very Marginal Donors in Switzerland

Christian Kuhn 1, Brian Lang 2, Sylvia Lörcher 1, Andrea Karolin 1, Isabelle Binet 3, Délaviz Golshayan4, Karine Hadaya 5, Thomas Müller 6, Stefan Schaub 2, Franz Immer 7, Michael Koller 2, Daniel Sidler 1

***1.** Klinik für Nephrologie und Hypertonie, Inselspital, Bern, Bern, Switzerland **2.** Klinik für Transplantationsimmunologie und Nephrologie, Universitätsspital Basel, Basel, Switzerland **3.** Klinik für Nephrologie und Transplantationsmedizin, Kantonsspital St. Gallen, St. Gallen, Switzerland **4.** Centre de transplantation d'organes et Service de néphrologie, Centre hospitalier universitaire vaudois, Lausanne, Switzerland **5.** Service de néphrologie et hypertension, hôpitaux universitaires Genève, Genève, Switzerland **6.** Klinik für Nephrologie, Universitätsspital Zürich, Zürich, Switzerland **7.** Swisstransplant, the Swiss National Foundation for Organ Donation and Transplantation, Bern, Switzerland*

Background

Kidney transplantation from marginal donors is an effective means to confront organ shortage. However, only little research has been done on very marginal kidney donors (VMD), e.g. 70 years of age or more. We examined patient and graft outcome of renal transplantation from VMD in Switzerland, using the Swiss Transplant Cohort Study (STCS) and Swiss Organ Allocating System (SOAS).

Methods

We evaluated the outcome of 1726 adult recipients of deceased donor transplantations from VMD from 2008 to 2019; median follow-up was 3.1 years. Failure-free survival (freedom from graft loss and death) was analyzed depending on donor age as a continuous variable as well as for three distinct donor groups, namely standard donors (reference group, age <60 years, n = 1033), marginal donors (MD, 60.1-70 years, n = 428) and very marginal donors (VMD, >70.1 years, n = 265). Furthermore, achieved transplant function (eGFR at 1 year) was analyzed and compared between these three groups.

Results

Failure-free survival decreased with increasing donor age, with a steep surge for donors older than 65 years, leading to a hazard ratio of 1.4 for graft loss or death for VMD aged 70 years and 3.2 for VMD aged 80 years, compared to a reference donor of 41 years. This increased risk of treatment failure was mainly attributed to premature graft loss. Still, Kaplan Meier Analysis revealed an acceptable patient and allograft outcome with a 5 year failure-free survival of 82.8%, 80.4% and 65.9% for the SD, MD, and VMD subgroups, respectively. eGFR 12 months post-TPL was significantly higher in SD compared to MD and VMD transplantation with an average eGFR of 59.6, 46.4 and 39.1 ml/min/1,73 m^2 for SD, MD and VMD, respectively.

Conclusions

Deceased donor kidney transplantation from donors aged 70 years or older is associated with an inferior, yet acceptable failure-free outcome.

OC 10

Targeting Malt1-dependent TCR downstream signaling to promote experimental allograft survival

Lerisa Govender 1, Josip Mikulic 1, Jean-Christophe Wyss 1, Olivier Gaide 2, Margot Thome 3, Dela Golshayan 4

***1.** Transplantation Immunopathology Lab, CHUV, Lausanne, Switzerland **2.** Dermatology , CHUV, Lausanne, Switzerland **3.** Department of Biochemistry, UNIL, Lausanne, Switzerland **4.** Transplantation Immunopathology Lab and Transplantation Center, CHUV and UNIL, Lausanne, Switzerland*

Background Strategies targeting T cells are the cornerstone of immunosuppression after solid organ transplantation. The transcription factor NF-κB is a key regulator of downstream T-cell activation and induction of inflammatory mediators; its full activation via antigen receptor engagement requires both the scaffold and the protease activity of the paracaspase Malt1. Recent studies have highlighted that Malt1-deficient mice were resistant to experimental autoimmune encephalomyelitis, although they lacked peripheral regulatory T cells (Treg).

Methods

Here, we compared targeting Malt1 versus using calcineurin inhibitors as immunosuppression in a stringent experimental transplantation model.

Results

Using transgenic mice, we found that Malt1-deficiency impaired Th1-mediated alloresponses *in vitro* and *in vivo,* and significantly prolonged MHC-mismatched skin allograft survival, compared to cyclosporine. However, it paradoxically enhanced Th17 differentiation in our transplantation setting. Interestingly, more selective inhibition of Malt1 protease activity in wild-type mouse and human peripheral T cells *in vitro* led to attenuation of alloreactive Th1 cells, while preserving preexisting Treg in the peripheral T-cell pool, and without promoting Th17 differentiation.

Conclusions

Thus, there is a place for further investigation of the role of Malt1 signaling in the setting of solid organ transplantation.

OC 11

Pre-transplant donor-specific HLA antibodies and risk for poor first year renal transplant outcomes – Results from the Swiss Transplant Cohort Study

Caroline Wehmeier 1, Patrizia Amico 1, Daniel Sidler 2, Urs Wirthmüller 3, Karine Hadaya 4, Jean Villard 5, Manuel Pascual 6, Vincent Aubert 7, Aurelia Schnyder 8, Kata Sunic 8, Thomas Müller 9, Jakob Nilsson 10, Stefan Schaub 1

***1.** Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, Basel, Switzerland **2.** Department of Nephrology and Hypertension, Inselspital, Berne University Hospital and University of Berne, Berne, Switzerland **3.** Department of Laboratory Medicine, Inselspital, Berne University Hospital and University of Berne, Berne, Switzerland **4.** Divisions of Nephrology and Transplantation, Geneva University Hospitals, Geneva, Switzerland **5.** Transplantation Immunology Unit, Service of Immunology and Allergy and Service of Laboratory Medicine, Geneva University Hospital and Medical School, Geneva, Switzerland **6.** Transplantation Center, Lausanne University Hospital, Lausanne, Switzerland **7.** Division of Immunology and Allergy, Lausanne University Hospital, Lausanne, Switzerland **8.** Department of Nephrology and Transplantation Medicine, Kantonsspital St. Gallen, St. Gallen, Switzerland **9.** Division of Nephrology, University Hospital Zurich, Zurich, Switzerland **10.** Department of Immunology, University Hospital Zurich, Zurich, Switzerland*

Background

Presence of pre-transplant donor-specific HLA antibodies (DSA) is a well established risk factor for inferior allograft survival on the long-term but may also negatively impact short-term transplant results. The aim of this study was to analyze first year renal outcomes in an unselected Swiss multicenter cohort having precise DSA assignment.

Methods

Data of the Swiss Transplant Cohort Study comprising 2215 renal transplants performed between 2008 and 2017 were investigated. All transplants had a complete virtual crossmatch. The investigated composite endpoint was a poor first year outcome defined as (i) allograft failure or (ii) death or poor allograft function (eGFR ≤25 ml/min/1.73 m^2) at one year.

Results

In total, 411 (19%) transplants had pre-transplant DSA. Two hundred twenty-one (10%) transplants showed a poor first year outcome. While rejection (24/70; 34%) was the most common reason for graft failure, infections (18/48; 38%) were the leading cause of death. First year patient's death was overall rare (48/2215; 2%). There were no significant differences between DSA-positive and DSA-negative transplants regarding the composite outcome, each individual outcome as well as reasons for graft failure and death. However, DSApositive transplants experienced more frequently rejection episodes, which was driven by a higher frequency of antibody-mediated rejection (both p <0.0001) compared with DSA-negative transplants. When investigating graft survival according to occurrence of rejection in DSA-positive and DSA-negative transplants, the combination of pre-transplant DSA and any first year rejection was associated with the overall poorest death-censored allograft survival (p <0.0001).

Conclusions

Presence of pre-transplant DSA per se does not affect first year renal transplant outcomes. However, DSApositive transplants experiencing rejection within the first year post-transplant are a high-risk population for poor allograft survival and may benefit from intense surveillance and early rejection treatment.

OC 12

Long term follow-up of ABO-incompatible kidney transplantation in Freiburg i. Br. – a single centre outcome report

Christina Langhorst [1], Bernd Jänigen [2], Stefan Zschiedrich [3]

1. Faculty of Medicine, University of Freiburg, Freiburg, Germany 2. Department of General and Digestive Surgery, Medical Centre - University of Freiburg, Freiburg, Germany , 3. Nephrology, Department of Internal Medicine, Bürgerspital, Solothurn, Switzerland

Background ABO-incompatible kidney transplantation (ABOi-KT) is an established way to enlarge the donor pool around the world. Comparability of long-term success and complications to ABO-compatible kidney transplantation (ABOc-KT) are still under debate.

Methods

We evaluated all patients with a living donor kidney transplantation performed between April 1st, 2004 and March 31st, 2019.

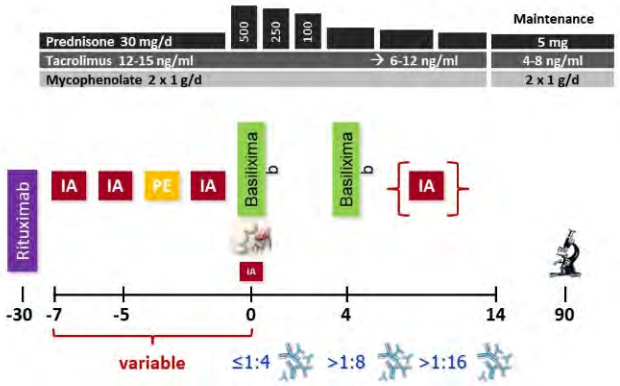
Results

A total of 137 ABOi-KT and 346 ABOc-KT were analysed. We excluded 4 ABOi-KT recipients and 178 ABOc-KT recipients with cyclosporine A-based immunosuppression or without basiliximab induction. 3 patients of the ABOi-KT cohort and 6 patients of the ABOc-KT cohort were lost to follow-up and therefore excluded. The patient characteristics were comparable except for the higher age of transplant recipients in the ABOc-KT cohort and longer follow-up of the ABOi-KT cohort. The mean estimated 15-year recipient survival was 89% in the ABOi-KT and 91% in the ABOc-KT cohort (p = 0.39). Mean estimated graft survival was 71% in the ABOi-KT and 87% in the ABOc-KT cohort (p = 0.68). The estimated GFR (MDRD) measured in the last follow-up was 51 ml/min/1.73 m^2 in the ABOi-KT cohort and 50 ml/min/1.73 m^2 in the ABOc-KT cohort (p = 0.36). The incidence for antibody-mediated rejection, T cell-mediated rejections and infectious complications requiring hospitalization was not different between both cohorts. In the ABOi-KT cohort, we found significantly more lymphoceles and consequent surgical revision procedures.

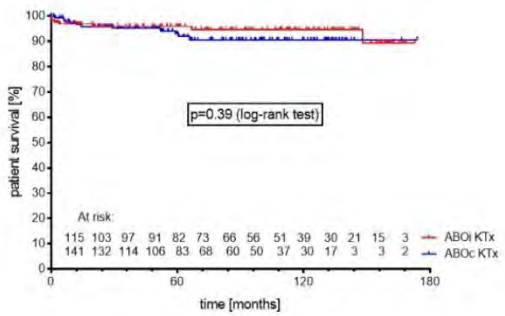
Conclusions

At Freiburg i. Br. University Medical Centre, ABOi-KT has as good long-term results as ABOc-KT in terms of patient survival, graft survival, and complications, with the exception of increased lymphocele formation.

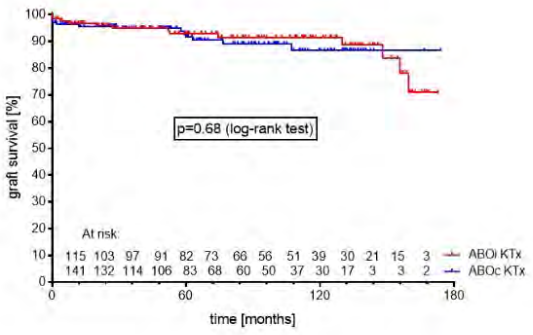
ABOi-KT protocol



Patient survival



Graft survival



ORAL COMMUNICATIONS – CLINICAL NEPHROLOGY / HYPERTENSION / MINERAL / ELECTROLYTES

OC 13

Validation of blood pressure measurements with the OptiBP smartphone app against auscultatory measurements

Patrick Schoettker 1, Arlène Wuerzner 2, Jean Degott 1, Gregory Hoffman 1, Martin Proença 3, Guillaume Bonnier 3, Alia Lemkaddem 3, Mathieu Lemay 3, Raoul Schorer 4, Urvan Christen 5, Jean Francois Knebel 5, Grégoire Wuerzner 6

1. *Service d'anesthésiologie, Lausanne University Hospital and University of Lausanne, Switzerland* ***2.*** *Service of Nephrology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland* ***3.*** *CSEM, Swiss Center for Electronics and Microtechnology, Neuchâtel, Switzerland* ***4.*** *Department of Acute Medicine, Geneva University Hospital and University of Geneva, Geneva, Switzerland* ***5.*** *Biospectal SA, 1003 Lausanne, Switzerland* ***6.*** *Nephrology and Hypertension Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland*

Background

Mobile health diagnostics have been shown to be effective and scalable for chronic disease detection and management. Maximizing the smartphones' optics and computational power could allow assessment of physiological information from the morphology of pulse waves and thus estimate cuffless blood pressure (BP).

Methods

We trained the parameters of an existing pulse wave analysis algorithm (oBPM™), previously validated in anaesthesia on pulse oximeter signals, by collecting optical signals from 51 patients fingertips via a smartphone while simultaneously acquiring BP measurements through an arterial catheter. We then compared smartphone-based measurements obtained on 50 participants in an ambulatory setting via the OptiBP app against simultaneously acquired auscultatory systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP) measurements.

Results

Patients were normotensive (70.0% for SBP versus 61.4% for DBP), hypertensive (17.1% vs. 13.6%) or hypotensive (12.9% vs. 25.0%). The difference in BP (mean ± standard deviation) between both methods were within the ISO 81060-2:2018 standard for SBP (-0.7 ± 7.7 mmHg), DBP (-0.4 ± 4.5 mmHg) and MBP (-0.6 ± 5.2 mmHg).

Conclusions

These results demonstrate that BP can be measured with accuracy at the finger using the OptiBP smartphone app. This may become an important tool to detect hypertension in various settings, for example in low-income countries, where the availability of smartphones is high but access to health care is low.

OC 14

Circular RNA-based biomarkers in blood of patients with Fabry Disease and related phenotypes

Albina Nowak 1, George Haddad 1, Andreas Kistler 2, Stellor Nlandu-Khodo 3, Felix Beuschlein 1, Rudolf Wüthrich 1, Johan Lorenzen 1, Malte Koelling 1

1. *University Hospital of Zurich, Zurich, Switzerland* ***2.*** *Cantonal Hospital Frauenfeld, Frauefeld, Switzerland* ***3.*** *University of Zuric, Zurich, Switzerland*

Background

Fabry disease is a rare X-linked lysosomal storage disease caused by mutations in the galactosidase α gene. Deficient activity of α-galactosidase A leads to glycosphingolipid accumulations in multiple organs. Circular RNAs represent strong regulators of gene expression. Their circular structure ensures high stability in blood. We hypothesized that blood-based circular RNA profiles improve phenotypic assignment and therapeutic monitoring of Fabry Disease.

Methods

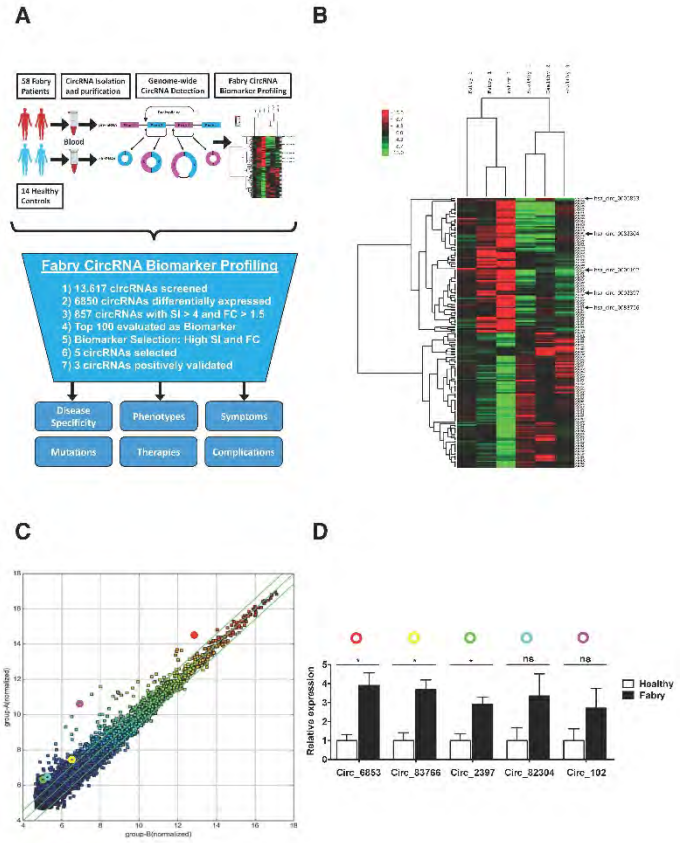
A genome-wide circular RNA expression analysis was performed in blood of genetically diagnosed patients

with Fabry Disease (n = 58), age- and sex matched healthy volunteers (n = 14) and disease control patients with acute kidney injury (n = 109). Most highly dysregulated circular RNAs were validated by quantitative real-time polymerase chain reaction. Circular RNA biomarker sensitivity, specificity, predictive values and AUC were determined. Linear regression analyses were conducted for validated circular RNA biomarkers and clinical patient characteristics.

Results

A distinct circular RNA transcriptome signature identified patients with Fabry Disease (Figure 1).

Figure 1



Level of circular RNAs *hsa_circ_0006853* (AUC = 0.73), *hsa_circ_0083766*(AUC = 0.8) and *hsa_circ_0002397* (AUC = 0.8) distinguished patients with Fabry Disease from both healthy controls and patients with acute kidney injury (Figure 2); the hsa_circ_0006853 tended to be more up-regulated in males then in females and in classic then in lateronset phenotype patients; the hsa_circ_0002397 was significantly more up-regulated in females then in males and in classic then in lateronset phenotype patients (Figure 2). *Hsa_circ_0002397* was, furthermore, female-specifically expressed. Circular RNA level were significantly related to galactosidase α gene mutations, early symptoms, phenotypes, disease severities, specific therapies and long-term complications of Fabry Disease (Table 1).

Conclusions

The discovery of circular RNA-based and Fabry Disease-specific biomarkers may advance future diagnosis of Fabry Disease and help to distinguish related phenotypes

Figure 2

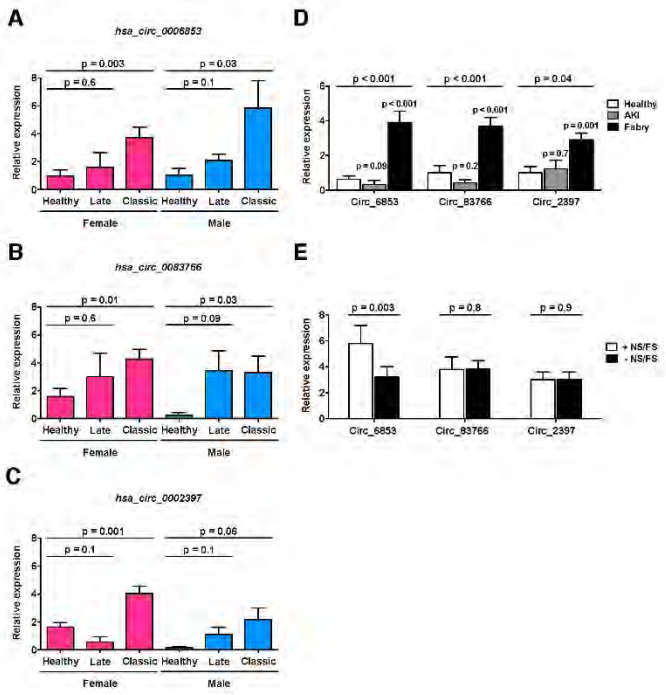


Table 1. Linear regression of blood circular RNA level as dependent variable

	Circular RNA	β (95% CI)	Univariate *P* value	Multivariate *** *P* value
Disease severity				
Classic phenotype	*hsa_circ_0006853*	3.89 (2.60-5.19)	<0.001	
	hsa_circ_0083766	3.78 (2.22-4.74)	<0.001	
	hsa_circ_0002397	3.07 (2.18-3.96)	<0.001	
Sex male	*hsa_circ_0006853*	3.92 (1.53-6.30)	0.002	
	hsa_circ_0083766	3.33 (1.04-5.61)	0.005	
	hsa_circ_0002397	1.78 (-0.33-3.89)	0.10	
Age	*hsa_circ_0006853*	0.02 (-0.001-0.001)	0.91	
	hsa_circ_0083766	0.04 (0.00-0.001)	0.82	
	hsa_circ_0002397	0.78 (0.05-0.08)	<0.001	0.04
More severe genotype *	*hsa_circ_0006853*	4.93 (2.25-7.61)	0.001	0.02
	hsa_circ_0083766	3.80 (1.05-6.54)	0.008	
	hsa_circ_0002397	3.11 (0.86-5.36)	0.008	
LysoGb3 in DBS	*hsa_circ_0006853*	0.09 (0.03-0.15)	0.003	
	hsa_circ_0083766	0.06 (0.01-0.12)	0.02	
	hsa_circ_0002397	0.09 (0.03-0.15)	0.003	
On specific therapy **	*hsa_circ_0006853*	4.09 (2.64-5.55)	<0.001	0.07
	hsa_circ_0083766	4.10 (2.79-5.42)	<0.001	0.02
	hsa_circ_0002397	2.92 (1.69-4.15)	<0.001	
Early signs and symptoms				
Neuropathic pain	*hsa_circ_0006853*	4.70 (3.05-6.36)	<0.001	0.001
	hsa_circ_0083766	4.11 (2.46-5.77)	<0.001	0.01
	hsa_circ_0002397	3.36 (1.95-4.78)	<0.001	0.01
Hypohidrosis	*hsa_circ_0006853*	3.93 (1.55-6.32)	0.002	0.047
	hsa_circ_0083766	3.10 (0.70-5.50)	0.01	
	hsa_circ_0002397	3.14 (1.15-5.13)	0.003	
Angioceratoma	*hsa_circ_0006853*	3.74 (1.26-6.22)	0.004	
	hsa_circ_0083766	4.19 (1.87-6.51)	0.001	0.04
	hsa_circ_0002397	3.57 (1.56-5.59)	0.001	0.02
Cornea verticillata	*hsa_circ_0006853*	4.09 (2.53-5.66)	<0.001	0.005
	hsa_circ_0083766	3.72 (2.20-5.23)	<0.001	
	hsa_circ_0002397	3.14 (1.94-4.34)	<0.001	0.02
Disease complications				
Nephropathy	*hsa_circ_0006853*	3.95 (1.88-6.02)	<0.001	
	hsa_circ_0083766	3.98 (2.04-5.92)	<0.001	
	hsa_circ_0002397	3.09 (1.28-4.89)	0.001	
Estimated GFR†	*hsa_circ_0006853*	0.64 (0.03-0.05)	<0.001	
	hsa_circ_0083766	0.68 (0.02-0.05)	<0.001	
	hsa_circ_0002397	0.78 (0.02-0.04)	<0.001	0.04
Serum creatinine	*hsa_circ_0006853*	0.02 (0.01-0.03)	0.001	
	hsa_circ_0083766	0.02 (0.01-0.03)	<0.001	0.01
	hsa_circ_0002397	0.01 (0.002-0.02)	0.01	
Protein/creatinine ratio, urine	*hsa_circ_0006853*	69.1 (21.9-116.3)	0.005	
	hsa_circ_0083766	86.3 (37.1-135.5)	0.001	
	hsa_circ_0002397	105.8 (49.5-162.2)	0.001	
Cardiomyopathy	*hsa_circ_0006853*	2.87 (0.46-5.28)	0.02	
	hsa_circ_0083766	4.19 (2.14-6.23)	<0.001	
	hsa_circ_0002397	2.76 (1.04-4.48)	0.003	
LVMMI	*hsa_circ_0006853*	0.03 (0.02-0.05)	<0.001	0.03
	hsa_circ_0083766	0.04 (0.03-0.05)	<0.001	0.005
	hsa_circ_0002397	0.03 (0.02-0.03)	<0.001	
Cerebrovascular disease	*hsa_circ_0006853*	5.75 (0.67-10.82)	0.03	
	hsa_circ_0083766	4.79 (-0.18-9.76)	0.06	

OC 15

ILLUMINATE-A, a phase 3 study of lumasiran, an investigational RNAi therapeutic, in children and adults with primary hyperoxaluria type 1 (PH1)

Sander Garrelfs [1], Yaacov Frishberg [2], Sally Hulton [3], Michael Koren [4], William O'Riordan [5], Pierre Cochat [6], Georges Deschenes [7], Hadas Shasha-Lavsky [8], Jeffrey Saland [9], William van't Hoff [10], Daniel G. Fuster [11], Daniella Magen [12], Shabbir Moochhala [13], Gesa Schalk [14], Eva Simkova [15], Jaap Groothoff [1], David Sas [16], Kristin Meliambro [9], Jiandong Lu [17], Pushkal Garg [17], John Gansner [17], Tracy McGregor [17], John Lieske [16]

***1.** Amsterdam UMC, Department of Pediatric Nephrology, Amsterdam, The Netherlands **2.** Shaare Zedek Medical Center, Division of Pediatric Nephrology, Jerusalem, Israel **3.** Birmingham Children's Hospital, Department of Nephrology, Birmingham, Great Britain **4.** Jacksonville Center for Clinical Research, Jacksonville, The United Stateds **5.** eStudySite **6.** Hospices Civils de Lyon and Université de Lyon, Centre for Rare Renal Diseases & Inserm Pediatric Clinical Investigation Centre, Lyon France **7.** Hospital Robert Debré, Department of Pediatric Nephrology, Paris, France **8.** Galilee Medical Center, Nahariya, Israel **9.** Icahn School of Medicine, New York, The United States **10.** Great Ormond Street Hospital, Department of Pediatric Nephrology, London, Great Britain, **11.** Division of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland , **12.** Rambam Health Care Campus, Department of Pediatric Nephrology, Haifa, Israel **13.** Royal Free Hospital, London, Great Britain **14.** University of Bonn, Bonn, Germany **15.** Al Jalila Children's Hospital, Dubai, United Arab Emirates **16.** Mayo Clinic, Rochester, The United States, **17.** Alnylam Pharmaceuticals, Cambridge, The United States*

Background

PH1 is a rare genetic disorder characterized by hepatic oxalate overproduction, leading to recurrent kidney stones, nephrocalcinosis, progressive kidney failure, and multiorgan damage from systemic oxalosis. There are no approved pharmacologic therapies for PH1. Lumasiran is a subcutaneously-administered investigational RNAi therapeutic that targets glycolate oxidase to reduce hepatic oxalate production. We report the first results from the six-month, double-blind period of ILLUMINATE-A, a randomized, placebo-controlled Phase 3 study to evaluate lumasiran in patients with PH1.

Methods

Key inclusion criteria: age≥6 years, 24hr urinary oxalate (UOx)≥0.70 mmol/24hr/1.73 m^2, confirmed PH1 diagnosis, eGFR ≥30 mL/min/1.73 m^2. Randomization: 2:1; lumasiran (n = 26), placebo (n = 13). Dosing: 3 mg/kg monthly ×3, then quarterly. Primary endpoint: percent change in 24 hr UOx excretion from baseline to month (M) 6. Primary comparison: least square (LS) mean treatment difference in percent change from baseline (average of M3-6).

Results

Lumasiran led to a statistically significant percent reduction in 24hr UOx excretion compared to placebo: the LS mean change from baseline to M6 (average of M3-6) was −65.4% with lumasiran and −11.8% with placebo (LS mean difference: −53.5%; p = 1.7×10−14). Subgroup analyses of the primary endpoint showed a consistent effect of lumasiran across age, baseline UOx, eGFR, and concomitant pyridoxine use. Lumasiran led to statistically significant improvements in all hierarchically tested secondary endpoints, including: proportion of lumasirantreated patients that achieved normalization or near-normalization of 24hr UOx at M6 (84% vs 0% of placebotreated patients, p = 8.3×10−7), and percent change in plasma oxalate from baseline to M6 (average of months 3-6) (-39.5%, p = 2.9×10−8). There were no serious or severe adverse events. The most common adverse events related to lumasiran were mild, transient injection site reactions.

Conclusions

Lumasiran resulted in clinically meaningful, rapid, sustained, and statistically significant reductions in urinary and plasma oxalate levels compared to placebo during the 6-month double-blind period. Lumasiran has a favorable safety profile.

OC 16

Roxadustat for the treatment of anemia in chronic kidney disease (CKD) patients not on dialysis (NDD): a phase 3, randomized, open-label, active-controlled study

Jonathan Barratt 1, Branislav Andric 2, Avtandil Tataradze 3, Michael Schömig 4, Michael Reusch 5, Udaya Valluri 5

***1.** Department of Cardiovascular Sciences, University of Leicester, Leicester, UK, **2.** Department of Nephrolog Department ofNephrology and Dialysis, Health Center Krusevac, Serbiay and Dialysis, Health Center Krusevac, Serbia **3.** Dialysis, Nephrology andTransplantation Union of Georgia, National Center of Urology, Georgia **4.** Center for Dialysis and Nephrology, Heilbronn andNeckarsulm, Germany **5.** Development Medical Science, Astellas Pharma Europe B.V.*

Background

Roxadustat is an orally administered hypoxia-inducible factor prolyl hydroxylase inhibitor for the treatment ofanemia in CKD patients. Efficacy and safety of roxadustat versus darbepoetin alfa (DA) were assessed in NDDCKD patients in a randomized, open-label, active-controlled phase 3 study.

Methods

NDD CKD patients with anemia were randomized to roxadustat or DA for up to 2 years. Doses were titrated tocorrect and maintain hemoglobin (Hb) within 10–12 g/dL. The primary endpoint was Hb response, defined asHb ≥11.0 g/dL and Hb increase from baseline of ≥1.0 g/dL in patients with baseline Hb >8.0 g/dL, or an increase of ≥2.0 g/dL in patients with baseline Hb ≤8.0 g/dL, during the first 24 weeks of treatment without rescue therapy. The noninferiority margin for roxadustat was -15%. Key secondary endpoints included change in low-density lipoprotein (LDL) cholesterol, time to first IV iron use, change in mean arterial pressure (MAP), and occurrence of hypertension. Treatment-emergent adverse events (TEAEs) were assessed.

Results

Of 616 randomized patients (roxadustat, 323; DA, 293), 424 completed treatment (roxadustat, 215; DA, 209).Mean baseline Hb was 9.55 g/dL in both groups. The proportion of patients who achieved the defined Hb response during the first 24 weeks was 89.5% (roxadustat; n = 256/286) and 78.0% (DA; n = 213/273), with a difference of 11.51% (95% CI: 5.66%, 17.36%), thereby establishing roxadustat's noninferiority to DA. Noninferiority of roxadustat to DA was demonstrated for MAP and time to occurrence of hypertension. Superiority of roxadustat to DA was demonstrated for decreasing LDL cholesterol and increasing time to first IV iron use. The incidence of TEAEs was comparable between roxadustat (91.6%) and DA (92.5%).

Conclusions

Roxadustat was noninferior to DA for Hb response during the first 24 weeks of treatment in NDD CKD patients. Safety profiles were comparable between groups.

OC 17

Are antihypertensive drugs associated with an increased risk of positive SARS-CoV-2 nasal swab? A case-control study

Erietta Polychronopoulou 1, Virginine Durgnat 1, Peggy Marpt 1, Francois Veuve 2, Benoit Guery 3, Gilbert Greub 4, Murielle Bochud 5, Thierry Buclin 2, Grégoire Wuerzner 6

***1.** Service of Nephrology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland **2.** Service of clinical pharmacology, Lausanne University Hospital and University of Lausanne, Switzerland **3.** Infectious Diseases Service, Department of Medicine, University Hospital and University of Lausanne, Switzerland **4.** Centre for Research on Intracellular Bacteria, Institute of Microbiology, Lausanne University Hospital and University of Lausanne, Switzerland **5.** University Centre for General Medicine and Public Health, Lausanne, Switzerland **6.** Nephrology and Hypertension Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland*

Background

The angiotensin-converting enzyme 2 (ACE2) is the entry receptor of the SARS-CoV-2. The two antihypertensive drugs angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) have been shown to affect ACE2 expression in animal models and human cells. These reports have led to a controversy of the usefulness or the potential harmfulness of these drugs during the COVID-19 pandemic.

Methods

This was a case-control study. Patients with a diagnostic nasal swab test for SARS-CoV-2 at Lausanne University Hospital between March and July 2020 could be contacted to answer a questionnaire on antihypertensive drugs and cardiovascular risk. Odds ratios (OR) and 95% confidence intervals (95%CI) for associations between antihypertensive drugs and infection were estimated by logistic regression, while accounting for confounders.

Results

3554 tests from 3176 patients were available. We contacted 645 participants, of which 457 (348 positive tests – cases - and 109 negative tests - controls) gave their informed consent. Mean age was 47.6±16.5 years and mean body mass index was 25.8±4.9 kg/m^2. More women (62.1%) participated to the study. Among cases and controls, 8.8% reported diabetes, 13.0% were smokers, 16% reported hypercholesterolemia, 21.6% reported hypertension and 2.6% reported chronic kidney disease. Use of ARB (OR = 0.94; 95%CI 0.41-2.16) or ACEi (OR = 1.73; 95%CI 0.50-5.97) did not show any association with a positive nasal swab test. Calcium channel blockers, beta-blockers or diuretics were not associated with a positive test either. Of the cardiovascular risk factors, only smoking (OR = 0.35; 95%CI 0.19-064) was associated reduced odds of having a positive test.

Conclusions

This study confirms that, in Switzerland, ACEi and ARB are not associated with increased risk of SARS-CoV-2 infection. The apparent protection of smoking with SARS-CoV-2 infection within this University hospital setting needs further exploration.

OC 18

Acute Kidney Injury Increases the Risk for Subsequent Heart Failure Hospitalizations in Patients with Acute Dyspnea

Matthias Diebold 1, Tobias Zimmermann 2, Ivo Strebel 3, Desiree Wussler 2, Stefano Bassetti 2,*Christian Mueller 3, Tobias Breidthardt 2*

***1.** Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, Basel, Switzerland., **2.** Division of Internal Medicine, University Hospital Basel, University of Basel, Basel, Switzerland **3.** Cardiovascular Research Institute Basel, Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland*

Background

Acute kidney injury(AKI) is common and associated with increased mortality and morbidity. The impact of AKI on subsequent heart failure remains largely unknown.

Methods

The *Basics in Acute Shortness of Breath Evaluation Study*(BaselV) prospectively enrolled patients presenting the emergency department with acute dyspnea. Two independent specialists adjudicated the final cause of dyspnea. Serum creatinine concentrations were prospectively assessed throughout the hospitalization. AKI was defined according to the serum creatinine criteria of the 2012 KDIGO clinical practice guideline. AKI adjudication occurred blinded to the cause of dyspnea. Mortality and rehospitalizations were prospectively assessed during follow-up (median:768 days [IQR:290-950]). Renal recovery was defined as a discharge creatinine <1.25x baseline creatinine.

Results

AKI occurred in 809(40%) of 2021 patients and was associated with increased all-cause (adjusted Hazard Ratio [aHR] 1.33, 95%CI 1.13-1.55; p <0.01) and cardiovascular mortality (aHR 1.43, 95%CI 1.16-1.75; p <0.01). However, the impact of AKI on mortality was time-dependent with the highest impact on early 30-day mortality (aHR 2.47, 95%CI 1.62-3.76; p <0.01) (Figure 1A). AKI was not associated with all-cause or cardiovascular mortality in patients achieving renal recovery (p = 0.10 and p = 0.30). In contrast, AKI displayed a time-independent association with subsequent hospitalisations for heart failure (hHF) (aHR 1.49, 95%CI 1.15-1.94;p <0.01) (Figure 1B). The association with hHF was stronger for higher degrees of AKI (stage 2/3 aHR: 1.89; 95%CI 1.33-2.83; p <0.01). This association with hHF persisted in patients with non-cardiac dyspnea (aHR 2.43, 95%CI 1.05-5.59; p = 0.04), even after renal recovery (aHR 2.56, 95%CI 1.00-6.54; p = 0.05). Again, in patients with noncardiac dyspnea the association of advanced AKI (stage 2/3) with hHF was even stronger (aHR 4.25, 95%CI 1.59-11.36; p <0.01).

Conclusions

AKI independently increases the risk of hHF by almost 50%. This association persists in patients with noncardiac dyspnea, even after renal recovery by discharge. This suggests AKI to be a novel risk-factor for the development of clinically significant HF.

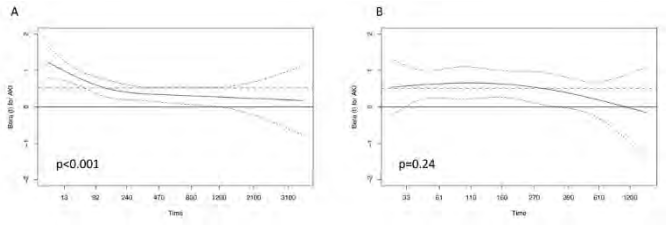


Figure 1 Smoothed plot of the coefficient β(t) for AKI and the prediction of all-cause mortality (A), heart failure rehospitalization (B). Red dotted horizontal line: fixed coefficient as determined by the cox model under proportional hazard assumptions. Black curved line: time-dependent behavior of the coefficient. Dotted curved lines: 95% confidence intervals. Straight black line: helper line at β(t) = 0 indicating the zero-effect level on the outcome. The p-Value results from the relationship between the Schoenfeld residuals and time. A significant relationship indicates a violation of the proportional hazard assumption.

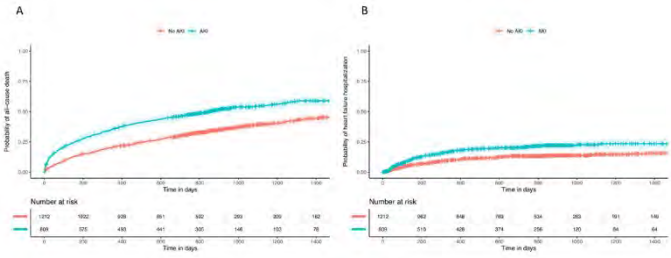


Figure 2 Kaplan Meier of AKI on overall mortality (A), heart failure hospitalization (B).

Variable	Overall (n=2021)	No AKI (n=1212)	AKI (n=809)	p-Value*
Demographics				
Age (median [IQR])	76 [66, 83]	75 [64, 82]	77 [68, 83]	<0.001
Male (%)	1154 (57)	706 (58)	448 (55)	0.216
Medical history				
Hypertension (%)	1415 (70)	800 (66)	615 (76)	<0.001
Coronary artery disease (%)	811 (40)	429 (35)	382 (47)	<0.001
CKD (%)	654 (32)	264 (22)	390 (48)	<0.001
Chronic heart failure (%)	612 (37)	320 (31)	292 (47)	<0.001
COPD/Asthma (%)	710 (35)	447 (37)	263 (33)	0.046
Active Smoking (%)	1313 (66)	806 (68)	507 (64)	0.072
Preadmission medication				
Angiotensin-converting enzyme inhibor (%)	647 (35)	352 (32)	295 (41)	<0.001
Angiotensin II receptor blocker(%)	356 (19)	209 (19)	147 (20)	0.432
Beta-Blocker (%)	842 (46)	451 (41)	391 (54)	<0.001
Aldosteron antagonist (%)	178 (10)	79 (7)	99 (14)	<0.001
Diuretic (%)	1061 (58)	548 (49)	513 (71)	<0.001
Statin (%)	626 (34)	358 (32)	268 (37)	0.030
Physical exam at ED				
sBP (mmHg)	137 [120, 156]	139 [124, 158]	133 [114, 152]	<0.001
HR (beats/min)	92 [76, 109]	94 [78, 110]	90 [74, 107]	0.001
Respiratory Rate (breaths/min)	22 [18, 28]	22 [18, 28]	22 [18, 28]	0.492
Temperature (°C)	37.2 [36.7, 37.7]	37.2 [36.7, 37.7]	37.2 [36.6, 37.8]	0.449
Oxygen saturation (%)	95 [92, 98]	96 [92, 98]	95 [91, 98]	0.121
Body mass Index (kg/m2)	25.8 [22.5, 29.6]	25.7 [22.4, 29.6]	25.8 [22.8, 29.5]	0.333
Laboratory parameters at admission				
Hemoglobin (g/l)	131 [116, 145]	135 [122, 147]	124 [109, 140]	<0.001
White blood celll count (10^9/l)	9.4 [7.2, 12.6]	9.2 [7.2, 12.1]	9.9 [7.3, 13.6]	0.004
C-reactive protein(mg/l)	17 [5, 54]	13 [5, 43]	22 [6, 70]	<0.001
NT-proBNP (ng/ml)	2036 [436, 6452]	1190 [274, 4466]	4147 [1292, 10603]	<0.001
Creatinine (µmol/l)	94 [72, 133]	82 [68, 105]	125 [94, 178]	<0.001
Baseline steady state creatinine (median [IQR])	77 [61, 102]	74 [60, 91]	84 [62, 120]	<0.001
Index diagnosis				
Cardiac Dyspnea (%)	1193 (59)	627 (52)	566 (70)	<0.001
COPD/Asthma (%)	410 (20)	296 (24)	114 (14)	<0.001
Pneumonia (%)	354 (18)	204 (17)	150 (19)	0.339
Viral/Influenza (%)	22 (1)	21 (2)	1 (0)	<0.001
Medication at discharge				
Angiotensin-converting enzyme inhibor (%)	837 (48)	510 (47)	327 (50)	0.166
Angiotensin II receptor blocker (%)	349 (20)	218 (20)	131 (20)	1.000
Beta-Blocker (%)	968 (55)	553 (51)	415 (63)	<0.001
Aldosteron antagonist (%)	301 (17)	177 (16)	124 (19)	0.150
Calcium Channel blocker (%)	381 (22)	223 (20)	158 (24)	0.072
Diuretic (%)	1225 (70)	699 (64)	526 (80)	<0.001
Statin (%)	700 (40)	419 (38)	281 (43)	0.062

Table 1: Baseline characteristics of all patients stratified by presence of acute kidney injury (AKI). AKI denotes acute kidney injury; CKD denotes chronic kidney disease; COPD denotes chronic obstructive pulmonary disease; sBP denotes systolic blood pressure; HR denotes heart rate; NT-BNP denotes N-terminal pro-brain natriuretic peptide; *p-Value are calculated between no-AKI and AKI. Values are numbers (percentages) or median [Interquantile range]

ORAL COMMUNICATIONS – HEMODIALYSIS / PERITONEAL DIALYSIS

OC 19

Relationship between dialysis adequacy, ultrafiltration rate and survival in young hemodialysis (HD) patients having initiated chronic HD in childhood

Verena Gotta [1], Olivera Marsenic [2], Andrew Atkinson [1], Marc Pfister [1]

1. *Pediatric Pharmacology and Pharmacometrics, University of Basel Children's Hospital, Basel Switzerland* , ***2.*** *Pediatric Nephrology, Stanford University School of Medicine, Lucile Packard Children's Hospital, Stanford, CA*

Background

Hemodialysis (HD) adequacy is currently assessed based on weight-normalized small solute clearance (spKt/V), with same targets in both adult and pediatric patients on chronic thrice weekly hemodialysis, despite lack of pediatric studies to support this. It has been hypothesised that pediatric patients of small size may require higher spKt/V targets, due to higher ratio of body surface area (BSA) to body weight and/or greater post-dialysis urea rebound. Ultrafiltration rates (UFR) >10-13 mL/kg/h, associated with increased mortality in adults, are furthermore routinely exceeded in pediatric patients with uncertain consequences. We aimed to characterize how different delivered HD adequacy metrics and UFR are associated with survival in a large cohort of patients who started HD in childhood.

Methods

Retrospective analysis on a cohort of patients <30y on chronic HD since childhood (<19y), having received thriceweekly HD 2004-2016 in outpatient DaVita dialysis centers. Mean delivered dialysis dose (spKt/V) and alternative measures of HD adequacy and fluid balance, including eKt/V, body-surface normalized Kt (Kt/BSA) and ultrafiltration rate (UFR), were investigated as predictors of survival in a Weibull regression model.

Results

A total of 1780 patients were included (age at initiation of HD: 0-12y: n = 321, >12-18y: n = 1459), with median spKtV = 1.55, eKt/V = 1.31, Kt/BSA = 31.2 L/m^2 and UFR = 10.6 mL/kg/h. Kt/BSA was a better predictor of survival than spKt/V or eKt/V (P<0.001 versus P = 0.002, respectively). UFR was associated with survival (P<0.001), with increased mortality <10/>18 mL/kg/h. Associations remained significant after adjusting for age, ethnicity, and etiology of kidney disease.

Conclusions

We found that targeting Kt/BSA>30 L/m^2 in children and young adults on maintenance HD is associated with improved long-term outcomes, corresponding to spKt/V>1.4 (>12 years) and >1.6 (<12 years), respectively. Relatively high UFR of 10-18 ml/kg/h appears to be risk-free in this HD population.

OC 20

COVID-19 pandemic in dialysis patients in Switzerland

Rebecca Winzeler [1], Patrice Ambühl [1]

1. *Institute of Nephrology, City Hospital Waid and Triemli, Zurich, Switzerland*

Background

COVID-19 is an infectious disease than can result from infection with the novel coronavirus SARS-CoV-2. The disease was first described in Wuhan at the end of 2019 and the first case in Switzerland was discovered in February 2020. This analysis gives an overview of dialysis patients in Switzerland that were tested COVID-19 positive.

Methods

All dialysis centers reported their cases with COVID-19 to the Swiss dialysis registry srrqap. All patients reported to the registry between March 5 (1st dialysis patient with COVID-19) and June 30, 2020 were included in this analysis and comparisons were made with COVID-19-free dialysis patients (from 2019).

Results

On March 5, 2020, the first dialysis patient was infected with COVID-19 in Ticino. The number of infected dialysis patients increased rapidly over the months of March and April, with the majority of patients in the cantons of Vaud (23.5%), Ticino (22.3%) and Geneva (18.8%) and together making up almost 65% of the COVID-19-infected dialysis patients in Switzerland. COVID-19 cases represented 2.4% of all prevalent patients on dialysis (as of 31.12.2019). Twenty-seven (12 female, 15 male) out of 93 dialysis patients died, which corresponds to a mortality rate of 29%. Mortality was highest in patients from Switzerland (together with the Netherlands), and lowest in Romania with 8.5% (K. Jager and A. Kramer, submitted for publication, 2020). Mortality was associated with advanced age in dialysis patients. In contrast to the general population, male sex, diabetes and hypertension were no major risk factors for mortality in our cohort.

Conclusions

Although dialysis patients from Switzerland in general have a better survival compared to those form other European countries, infection with COVID-19 in Switzerland results in the highest mortaliy compared to other European countries in this population. In addition, male sex, diabetes and hypertension seem not to be associated risk factors in our dialysis population.

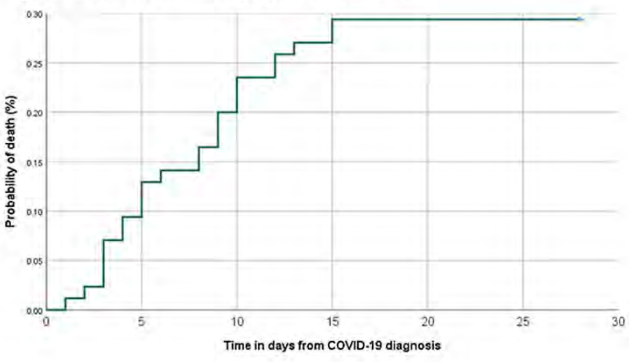
Table 1: Characteristics (given as mean±SD or percentage) in dialysis patients with COVID-19 and COVID-19-free dialysis patients

	With COVID-19 (n=93)	Without COVID-19 (n=4619)	p-value
Age, years	70.0 ± 15.5	68.9 ± 14.7	0.103
Male gender, %	65.6	65.2	0.898
Body mass index, kg/m²	27.3 ± 5.4	25.9 ± 5.7	0.228
Dialysis vintage, years	5.5 ± 12.7	4.0 ± 4.0	0.624
Dialysis duration per week (h)	11.4 ± 1.4	11.5 ± 1.4	0.749
Kt/V	1.55 ± 0.39	1.59 ± 0.41	0.259
Hemoglobin, g/dL	10.9 ± 1.4	11.1 ± 1.4	0.506
Ferritin, ng/mL	507 ± 416	510 ± 434	0.448
Calcium, mmol/L	2.21 ± 0.19	2.22 ± 0.19	0.822
Phosphate, mmol/L	1.50 ± 0.46	1.62 ± 0.48	0.769
PTH, ng/L	317.6 ± 238.2	369.2 ± 328.4	0.148
Comorbidities, n	2.9 ± 2.3	2.6 ± 2.0	0.047
CCI*	4.6 ± 2.2	4.5 ± 2.2	0.536
Hypertension, %	88.2	83.1	0.209
Diabetes Mellitus, %	43.5	37.7	0.273
Iron substitution, %	78.8	72.7	0.207
EPO substitution, %	81.2	79.7	0.732

Table 2: Characteristics (given as mean±SD or percentage) in dialysis patients with COVID-19 according to their survival status

	Non-Survivors, n=25	Survivors, n=60	p-value
Age, years	80.1 ± 7.4	65.1 ± 16.6	0.000
Male gender, %	52.0	71.7	0.081
Body mass index, kg/m²	28.3 ± 6.4	26.9 ± 4.9	0.282
Dialysis vintage, years	3.7 ± 4.1	4.2 ± 3.4	0.798
Comorbidities, n	3.4 ± 1.7	2.7 ± 2.4	0.046
CCI*	4.9 ± 1.9	4.5 ± 2.3	0.341
Diabetes, %	44.0	43.3	0.955
Hypertension, %	76.0	93.3	0.024

Figure 1: Probability of death in dialysis patients in Switzerland



OC 21

Glycine increases fat-free mass in chronic hemodialysis patients as compared to branched chain amino acids: a randomized double-blind cross-over trial

Laurence Genton [1], Menno Pruijm [2], Catherine Stoermann-Chopard [3], Nicola Marangon [3], Julie Mareschal [1], Arlène Wurzner [2], Vladimir Lazarevic [4], Nadia Gaia [4], Patrice Cani [5], François Herrmann [6], Jacques Schrenzel [4]

1. *Clinical Nutrition, Geneva University Hospitals and University of Geneva, Geneva, Switzerland* ***2.*** *Nephrology and Hypertension Department, Lausanne Uni-*

*versity Hospital and University of Lausanne, Lausanne, Switzerland **3.** Nephrology, Geneva University Hospitals and University of Geneva, Switzerland **4.** Genomic Research Lab and Service of infectious diseases, Geneva University Hospitals and University of Geneva, Switzerland **5.** Louvain Drug Research Institute WELBIO, Metabolism and Nutrition Research Group, University of Louvain, UCLouvain, Brussels, Belgium **6.** Rehabilitation and geriatrics, Geneva University Hospitals and University of Geneva, Geneva, Switzerland*

Background

Low muscle mass is associated with negative outcome in chronic hemodialysis (HD) patients. Branched-chain amino acids (BCAA) may increase the muscle mass. This multi-center placebo-controlled double-blind randomized cross-over study aimed at studying the impact of BCAA on lean body mass.

Methods

We included 36 chronic HD patients, with plasma albumin <38g/L or dry body weight loss >5% of dry body weight, and dietary intakes <30 kcal/kg/d and <1g protein/kg/d. Patients received either oral BCAA (2x7g/d) or an isocaloric placebo consisting of glycine (2x7g/d) for 4 months (period 1), followed by a wash-out period of 1 month, and the opposite supplement (period 2). Primary outcome was lean body mass, measured by dual-energy X-ray absorptiometry, secondary outcomes were fat-free mass index measured by bioelectrical impedance (Nutrigard ®, Geneva formula)1, resting energy expenditure, dietary intake, physical activity and function, quality of life, and blood parameters. Analyses were performed by multiple mixed linear regressions including type of supplementation, months, period, sex and age as fixed effects and subjects as random intercepts.

Results

Twenty-seven compliant patients (61.2±13.7 yrs, 41% women) completed the study. The type of supplementation did not affect lean body mass index and body weight, but BCAA significantly decreased fat-free mass index, as compared to the placebo containing glycine (coeff -0.27, 95%CI -0.43 to -0.10, p = 0.002, respectively). BCAA intake increased plasma transthyretin (coeff 14.10, 95%CI 5.38 to 22.8, p = 0.002). BCAA and glycine intake had no effect on the other clinical parameters, blood chemistry tests or plasma amino acids.

Conclusions

BCAA did not improve lean body mass as compared to glycine. Unexpectedly, glycine improved fat-free mass in HD patients, as compared to BCAA. Whether long-term supplementation with glycine improves the clinical outcome remains to be demonstrated.

OC 22

Management of patients on maintenance dialysis during the SARS CoV-2 pandemic: a perspective from Geneva, Switzerland

Ido Zamberg [1], Thomas Mavrakanas [1], Thomas Ernandez [2], Vincent Bourquin [3], Michael Zellweger [4], Nicola Marangon [5], Françoise Raimbault [2], Rebecca Winzeler [6], Anne Iten [7], Pierre-Yves Martin [2], Patrick Saudan [2]

***1.** Division of General Internal Medicine, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland **2.** Division of Nephrology, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland, **3.** Dialysis Unit, Hôpital de la Tour, Meyrin, Switzerland, **4.** Dialysis Unit, Groupe médical d'Onex, Onex, Switzerland **5.** Dialysis Unit, MV santé, Geneva, Switzerland **6.** Institute of Nephrology, City Hospital Waid and Triemli, Zurich, Switzerland **7.** Infection Control Program, Geneva University Hospitals, Geneva, Switzerland*

Background

Patients on maintenance hemodialysis are at high risk for serious complications from COVID-19 infection including death. We present an overview of the local experience with dialysis units management and reorganization, local epidemiology and outcomes during the COVID-19 outbreak in Geneva, Switzerland.

Methods

All SARS-CoV-2 positive outpatients on maintenance dialysis were transferred from their usual dialysis facility to the Geneva University Hospitals dialysis unit to avoid creation of new clusters of transmission. Within this unit, appropriate mitigation measures were enforced as suggested by the institutional team for prevention and control of infectious diseases.

Results

From February 25 to May 18, 2020, 19 of 246 patients on maintenance dialysis were tested positive for SARS-CoV-2, representing an incidence rate of 97.6 cases per 100,000 person-days. Eighteen patients were on maintenance hemodialysis and one on peritoneal dialysis. Twelve of these infections were detected during the first two weeks after mitigation strategies were enforced. Most common symptoms were fever (89%), cough (84%) and fatigue (68%). Two patients required orotracheal intubation. Six patients on maintenance hemodialysis who had previously tested positive for SARS-CoV-2, all of them male, died (32%). Five deaths were COVID-19 related and one death was due to dialysis withdrawal at the patient's request.

Conclusions

Strict mitigation measures seemed to be effective to control infection spread among patients on maintenance dialysis. CoViD-19 infection is associated with a high fatality rate. Large scale epidemiological studies are needed to assess the efficacy of preventive measures in decreasing infection and mortality rate within the dialysis population.

OC 23

An algorithm for the evaluation of the routine monthly blood draws in hemodialysis

Edward Pivin [1], Isabelle Bassi [1], Daniel Teta [1]

***1.** Hôpital de Sion, Néphrologie, Sion, Switzerland*

Background

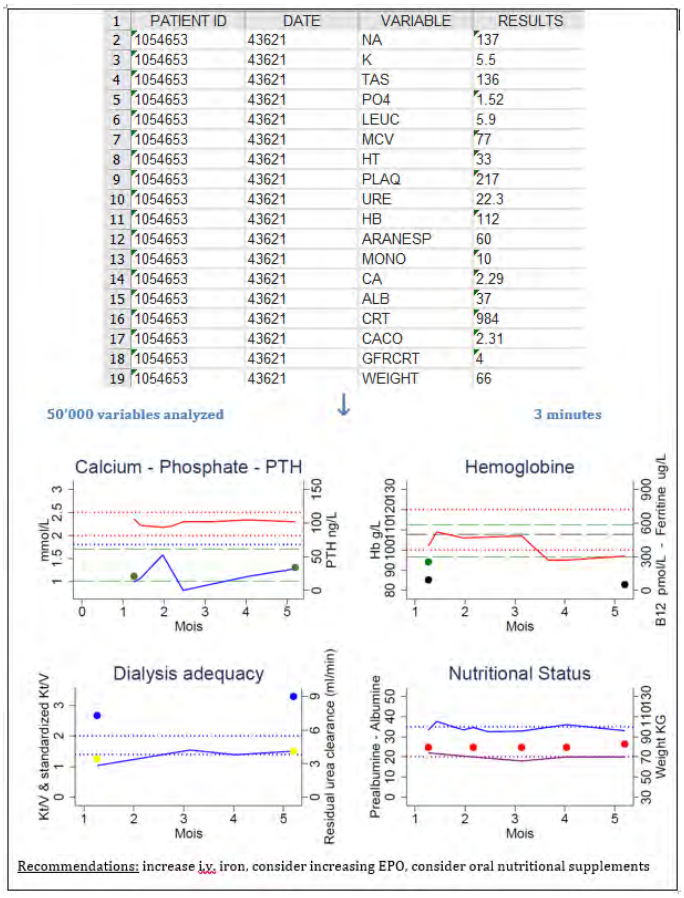
Laboratory testing in hemodialysis is performed every month in most centers. Results guide treatment of anemia, mineral and bone disorder, dietary recommendations and dialysis prescriptions. Its analysis is time consuming and its interpretation might be difficult and prone to error. We aimed to develop a rapid and accurate algorithm to analyze the results.

Methods

The algorithm consists of formulas, conditional statements, loops, graphs creation commands and generates alarms and treatment recommendations. Input: • An Excel sheet or a text file with four columns (patient ID, date, variable, result) with all available results, up to one billion lines.

Results

Output: • A list of all off targets laboratory results • KtV, residual kidney function, nPCR • Alarms (thrombopenia, leucopenia, low vitamin B12, hypoglycemia, abnormal liver enzymes…) and treatment recommendations (decrease EPO, increase i.v. iron, increase phosphate binders…) • Four graphs with results from the past six months to guide patient care (Figure 1)



Conclusions

We developed a rapid algorithm for the interpretation of the results of routine monthly blood draws in hemodialysis. Its utility and its time saving capacity needs to be validated in further studies.

OC 24

Estimation of access flow in fistulas and graft by duplex ultrasound imaging vs. intra-access flow volume testing in a single dialysis center

Clemens Jäger [1], Rüdiger Eisel [1], Alexandra Günther [1], Cäcilia Jäger [2], Aikatarina Benou-Petridis [1], Heinrich Heule [1]

1. *Nierenzentrum Rheintal-Liechtenstein, Altstätten, Schaan, Liechtenstein,* ***2.*** *Medical faculty, University Basel, Basel, Switzerland*

Background

Dialysis access function is significantly important for a successful hemodialysis. Methods for measuring access flow include different clinical tools such as imaging by Doppler ultrasound or intra-access flow measurement using ultrasound dilution (Transonic®).

Methods

We measured access flow in 39 hemodialysis patients (30 fistulas, 9 grafts). Two investigators performed independently each 3 duplex ultrasound measurements and the median value of the access flow was calculated. The volume flow (VF) measurements were performed using duplex instrument software calculation by the timeaveraged velocity (of Vmean) over a 3-pulse cycle x cross-sectional area. We stayed mainly in a longitudinal placement of the probe to determine this area. The intra-access flow was measured with the dilution technique by reversing the blood dialysis lines. Dilution was made with 10 ml saline and was measured by ultrasound sensors around the arterial and venous tubing lines. 3 measurements were done in one dialysis session with a maximum interval of 2 weeks to the ultrasound examinations.

Results

For reporting reasons, we split the measured flow volumes in a low flow (LF) <600 ml/min (n = 8), medium flow

(MF) 600–1500 ml/min (n = 24) and high flow (HF) >1500 ml/min (n = 6) group. The relative standard deviation of the 3 measurements by duplex ultrasound showed an overall spreading of 12.9% (LF 16.9%, MF 11.4%, HF 13.5%). When comparing the mean values of the measurements by intra-access dilution technique vs. duplex we established a deviation of 26% (LF 42%, MF 20%, HF 26%), whereas 19 were lower than the estimation by ultrasound, and 18 were higher.

Conclusions

Duplex ultrasound imaging and intra-access flow measurements are comparable and useful methods in the hands of a nephrologist. We favour the duplex ultrasound method as an accurate diagnostic technique because it allows besides flow measurements the assessment of shunt-anatomy and location of a possible access stenosis or thrombosis.

POSTER PRESENTATIONS – BASIC SCIENCE / GENETICS / EXPERIMENTAL NEPHROLOGY

P 1

Deletion of the Transcription Factor Prox-1 Specifically in the Renal Distal Convoluted Tubule Causes Hypomagnesemia via Reduced Expression of TRPM6 and NCC (NCCR project)

Christina Schnoz 1, Sandra Moser 1, Alexander Odermatt 2, Denise Kratschmar 2, Dominique Loffing-Cueni 1, Johannes Loffing 1

1. *1Institute of Anatomy, University of Zurich, 8057 Zurich, Switzerland ,* ***2.*** *2Division of Molecular and Systems Toxicology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland*

Background

The renal distal convoluted tubule (DCT) is critical for the fine-tuning of urinary ion excretion and the control of blood pressure. Ion transport along the DCT is tightly controlled by posttranscriptional mechanisms including a complex interplay of kinases, phosphatases, and ubiquitin ligases. Recently, we identified the transcription factor Prox-1 as a gene significantly enriched in the DCT of adult mice.

Methods

To test if Prox-1 contributes to the transcriptional regulation of DCT function and structure, we developed a novel mouse model (NCC^{cre}:$Prox\text{-}1^{flox/flox}$) for an inducible deletion of Prox-1 specifically in the DCT.

Results

The deletion of Prox-1 had no obvious impact on DCT-structure and growth independent whether the deletion was achieved in newborn or adult mice. Furthermore, DCT-specific Prox-1 deficiency did not alter DCTproliferation in response to loop-diuretic treatment. Likewise, the DCT-specific deletion of Prox-1 did not cause other gross phenotypic abnormalities. Body weight, urinary volume, $Na^+$and K^+ excretion as well as plasma Na^+, K^+ and aldosterone levels were similar in $Prox\text{-}1^{DCT\ KO}$ and $Prox\text{-}1^{DCT\ Ctrl}$ mice. However, $Prox\text{-}1^{DCT\ KO}$ mice exhibited a significant hypomagnesemia with a profound downregulation of the DCT-specific apical Mg^{2+} channel TRPM6 and the NaCl cotransporter (NCC) at both mRNA and protein levels. The expression of other proteins involved in distal tubule Mg^{2+} and Na+ handling was not affected.

Conclusions

Thus, Prox-1 is a DCT-enriched transcription factor that does not control DCT growth but contributes to the molecular control of DCT-dependent Mg^{2+} homeostasis in the adult kidney.

P 2

A five amino acid deletion in NKCC2 of C57BL/6 mice impacts detection of NKCC2 phosphorylation *

Sandra Moser 1, Yuya Sugano 2, Agnieszka Wengi 1, Viktoria Fisi 1, Lena Lindtoft Rosenbaek 3, Dominique Loffing 1, James A. McCormick 4, Robert A. Fenton 3, Johannes Loffing 2

1. *Institute of Anatomy, University of Zurich, Zurich, Switzerland* ***2.*** *Institute of Anatomy, Zurich, Switzerland* ***3.*** *Department of Biomedicine, Aarhus University, Aarhus, Denmark,* ***4.*** *Oregon Health & Science University Portland, Portland, The United States*

Background

The furosemide-sensitive Na^+-K^+-2Cl- cotransporter (NKCC2) of the thick ascending limb is critical for the renal control of electrolyte and fluid homeostasis. NKCC2 is activated via phosphorylation of several serine and threonine (T) residues in the N-terminal tail.

Methods

Several phosphoform-specific antibodies raised against these phosphorylation sites (e.g. T96 and T101) were developed to study NKCC2 activity and function in mice.

Results

In this study, strong pNKCC2 signals were detected in kidneys from 129Sv mice, but several anti pT96/pT101 NKCC2 antibodies did not detect pNKCC2 in kidneys from C57BL/6 mice. Nevertheless, cross-reactivity of the pNKCC2 antibodies with phosphorylated thiazide-sensitive NaCl cotransporter (pNCC) was evident. Likewise, pNCC antibodies showed cross-reactivity with pNKCC2 in 129Sv mice. Database analysis revealed that C57BL/6 mice have a five amino acid deletion (DF97-T101) in NKCC2 within the region of epitopes recognized by most pNKCC2 antibodies. While strain differences between 129Sv and C57BL/6 were evident in electrolyte excretion and renal transporter abundance profiles, cross breeding of the two strains indicated that the deletion does not segregate with phenotypic differences. To ensure reliable detection of phosphorylated NKCC2 in C57BL/6 mice, we developed a new phosphoform-specific antibody that recognizes pT96 NKCC2 independent of the mouse strain. In isolated kidney slices, lowering extracellular Cl- concentration increases phosphorylation of NKCC2 at T96. Changing extracellular K+ had no effect.

Conclusions

Our work reveals a hitherto not well appreciated, but essential, strain difference in the amino acid sequence of mouse NKCC2 that needs to be considered when analyzing NKCC2 and NCC phosphorylation. The newly developed pNKCC2 antibody circumvents these technical caveats.

** Student paper*

P 3

Single-nucleus RNA sequencing maps proximal tubule metabolic plasticity in acute kidney injury

Anna Rinaldi 1, David Legouis 2, Sophie De Seigneux 3, Pietro Cippà 4

1. *Ente Ospedaliero Cantonale, Division of Nephrology, Lugano, Switzerland* ***2.*** *Laboratory of Nephrology, Department of Medicine and Cell Physiology, University Hospital and University of Geneva, Geneva, Switzerland Division of Intensive Care, University Hospital of Geneva, Geneva, Switzerland ,* ***3.*** *Division of Nephrology, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland* ***4.*** *Division of Nephrology, Ente Ospedaliero Cantonale, Lugano, Switzerland*

Background

The kidney is a pivotal organ in the regulation of systemic metabolism and alterations of the metabolic functions of the kidney in response to acute kidney injury (AKI) are emerging as potential targets to improve renal outcome and AKI-associated mortality (Leguois et al. Nat Metabol 2020). We hypothesized that upon injury proximal tubule cells undergo to a coordinated transcriptome reprogramming, which modifies the metabolic function of the kidney.

Methods

We used single cell transcriptomics to generate a taxonomy of the metabolic properties of the proximal tubule along the transition from acute to chronic kidney injury. Data generated by our laboratory in mice were integrated with publicly available dataset of single-nucleus RNA sequencing. Different subsets of normal, repairing and injured proximal tubule cells were identified by established markers. Key genes of the metabolic cellular pathways were analysed over time in the different cell clusters.

Results

The transcriptomes of ca. 65'000 renal cells were analysed. Unsupervised sub-clustering of proximal tubule cells yielded 3 major subclusters representative of the normal S1, S2 and S3 segments and 3 more clusters expressing peculiar features associated to injury and repair. Analysis of the identified clusters across time points in UMAP space shows the temporal changes in gene expression and the identification of potential new cell states in the injured proximal tubule. Examination of the gluconeogenesis and glycolysis pathways confirmed the downregulation of the gluconeogenic genes after injury and the metabolic reprogramming to glycolysis. In addition, peculiar gene expression patterns involving NAD synthesis, fatty acid oxidation and amino acid metabolism were detected in different cell states.

Conclusions

These preliminary data are consistent with a coordinated metabolic reprogramming in proximal tubule cells in response to AKI.

P 4

NOSTONE Trial: Randomized double-blind placebo-controlled trial assessing the efficacy of standard and low dose hydrochlorothiazide treatment in the prevention of calcareous nephrolithiasis recurrence

Patrizia Amico 1, Giulia Bedino 2, Olivier Bonny 3, Christian Bucher 4, Florian Buchkremer 5, Grazia Cereghetti 6, Rosaria Del Giorno 7, Nasser A. Dhayat 8, Thomas Ernandez 9, Nicolas Faller 8, Luca Gabutti 10, Carina Huesler 11, Irene Koneth 4, Michael Mayr 1, Nilufar Mohebbi 12, Urs Odermatt 13, Lisa Pellegrini 14, Alexander Ritter 15, Beat Roth 16, Carlo Schönholzer 2, Harald Seeger 15, Catherine Stoermann-Chopard 9, Daniel Teta 17, Luca Tamò 6, Reto Venzin 18, Daniel Fuster 19

1. *Universitätsspital Basel, Transplantationsimmunologie und Nephrologie, Basel, Switzerland* ***2.*** *Division of Nephrology, Ente Ospedaliero Cantonale, Lugano, Switzerland ,* ***3.*** *CHUV, Service de Néphrologie, Lausanne, Switzerland* ***4.*** *Kantonsspital St. Gallen, Klinik für Nephrologie und Transplantationmedizin, St. Gallen, Switzerland* ***5.*** *Kantonalspital Aarau, Nephrologie, Dialyse und Transplantation, Aarau, Switzerland* ***6.*** *CTU Bern, University of Bern, Bern, Switzerland* ***7.*** *Ospedale regionale di Bellinzona e Valli, Bellinzona, Switzerland* ***8.*** *Inselspital, Bern University Hospital, University of Bern, Department of Nephrology and Hypertension, Bern, Switzerland* ***9.*** *HUG, Néphrologie, Genève, Switzerland* ***10.*** *Ospedale regionale di Bellinzona e Valli, Switzerland* ***11.*** *Hirslanden, Nierenpraxis und Dialyse, St. Gallen, Switzerland* ***12.*** *Universitätsspital Zürich, Klinik für dieNephrologie, Zürich, Switzerland* ***13.*** *Luzerner Kantonsspital, Nephrologie, Luzern, Switzerland* ***14.*** *Division of Nephrology, Ente Ospdaliero Cantonale, Lugano, Switzerland* ***15.*** *Universitätsspital Zürich, Klinik für Nephrologie, Zürich, Switzerlad* ***16.*** *CHUV, Service de Urologie, Lausanne, Switzerland* ***17.*** *Hôpital de Sion, Néphrologie, Sion, Switzerland* ***18.*** *Kantonsspital Graubünden, Dialyse / Nephrologie, Chur, Switzerland* ***19.*** *Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern and Department for BioMedical Research, University of Bern, Switzerland*

Background

Nephrolithiasis is a global healthcare problem with a current lifetime risk of up to 18.8% in men and 9.4% in women. Without specific treatment, 5- and 20-year recurrence rates are 40% and 75%, respectively. Given the high cost of medical treatments and surgical interventions as well as the morbidity related to symptomatic stone disease, medical prophylaxis for stone recurrence is an attractive approach. Nowadays, thiazides are widely used in the treatment of recurrent nephrolithiasis and arterial hypertension. In the case of recurrent nephrolithiasis, however, this practice is not supported by randomized evidence. Thus, evidence for benefits and harms of low dose thiazides in the prevention of calcium-containing kidney stones in general remains unclear.

Methods

The NOSTONE clinical trial is a multicenter, randomized, placebo-controlled, double-blind, parallel-group trial to assess the dose-response relationship for three different dosages of HCTZ (12.5mg, 25.0 mg, 50.0 mg). The primary outcome is the incidence of stone recurrence (a composite of symptomatic and radiologic recurrence); a low-dose CT will be performed at the beginning and at the end of the trial. The study aims to include 416 patients, recruited from 12 hospitals throughout Switzerland.

Results

Recruitment started in Bern on March 9th 2017; all study sites are operative since June 30th2017. All sites but Bern closed recruitment on August 31st 2019; Bern continued recruiting until October 31st 2019. The target number of 416 participants randomized in the trial was reached (regular updates: www.nostone.ch). Since March 2020, patients started completing the study according to schedule and the last patient's last visit will take place in August 2021.

Conclusions

The NOSTONE recruitment target was reached. The trial will end in August 2021, results are expected in early 2022. The NOSTONE study will provide long-sought information on the efficacy of hydrochlorothiazide in the recurrence prevention of calcium containing kidney stones.

P 5

Early experience with hypnosis treatment in patients with anxiety and pain symptoms while on hemodialysis

Sadegh Ebrahimzadeh 1, Gabriel Palacios 2, Liane Hornung Knauft 1, Michael Dickenmann 1, Anja Ulrich 3, Juerg Steiger 1, Melanie Schönenberger 1, Petra Künzler 1

1. *Universitätsspital Basel, Transplantationsimmunologie und Nephrologie, Basel, Switzerland* ***2.*** *Hypnose Zentrum Bern, Switzerland* ***3.*** *Departement Innere Medizin, Universitätspital Basel, Basel, Switzerland*

Background

Fear of shunt puncture, chronic pain, and nervousness are well known complaints in hemodialysis patients. Hypnosis is a complementary treatment option in patients suffering from these symptoms. Hypnotic trance allows communication with the subconscious and can induce mental relaxation. We report on first experience with hypnosis treatment in hemodialysis patients.

Methods

Patients suffering from fear, pain, and nervousness while on dialysis were addressed and informed about the effects and potential side effects of hypnosis treatment. Informed consent was obtained in all patients. Pharmacologic treatment was not modified during the hypnosis treatment. Treatment success was accessed by a 1-10 scale (numeric rating schale) of symptom relief with duration after treatment and a questionnaire after treatment. Applied hypnosis technique was chosen due to patient's symptoms and requests, either classic or modern hypnosis (method of Gabriel Palacios).

Results

Until now five hemodialysis patients were treated hypnosis. Patient 1: Suffering from general pain symptoms: symptom relief was 2 points on the scale during 4 hours. Patient 2: Suffering from severe pain by a necrotic limb wound: symptom relief was 4 points on the scale during 3 hours. Patient 3: Suffering from fear of shunt puncture: symptom relief was 2 points on the scale. Time of symptom relief was while puncture was performed. Patient 4: Suffering from restless legs: the patient observed no restless legs symptoms during hypnosis and 3 hours afterwards. Level of trance is 4 on Harry Arons Scale. Patient 5: Suffering from sleeplessness, nervousness, and perplexity: symptom relief during hypnosis until the following day. Level of trance is 4 on Harry Arons Scale.

Conclusions

Hypnosis in hemodialysis patients might offer a new, non-pharmacologic treatment option in patients suffering from fear, pain, and nervousness. Further studies are needed to gain more experience and a stable scientific basis.

P 6

Generating a mouse model with CRISPR/cas9 lacking the AU rich elements in TWEAK 3'UTR

Andrea Karolin 1, Stefan Rudloff 1, Daniel Sidler 2

1. *Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern and Department for BioMedical Research, University of Bern, Switzerland ,* ***2.*** *Inselspital, Bern University Hospital, University of Bern, Department of Nephrology and Hypertension, Bern, Switzerland*

Background

After kidney transplantation patients are treated with Calcineurin Inhibitors (CNI), such as Cyclosporine A and Tacrolimus as a maintenance immune suppression. However, long-term treatment with CNI leads to kidney disease characteristic for tubular atrophy, interstitial fibrosis and arteriohyalinosis. This disorders is partly driven via the pro-inflammatory TNF superfamily member TWEAK, since deficiency for this cytokine is sufficient to protect animals from CNT. Inflammatory genes are tightly regulated to ensure dynamic responses during inflammation and rapid resolution. Pro-inflammatory cytokines such as TNFα or G-CSF are controlled via post-transcriptional regulation. Specifically, regulatory proteins bind to specific AU-rich elements within the 3' UTR and regulate mRNA stability and subsequent transcription.

Methods

By using Luciferase Assay and CRISPR/cas9 genome editing, we researched the stability of the TWEAK mRNA.

Results

We identified AU-rich elements (ARE) within the 3' UTR of TWEAK and demonstrated that these sequences are critical in TWEAK regulation. Indeed, mutation or knock-out of these sequences increase mRNA half-life, transcription and activity. To decipher the biological relevance of this sequence, we established a mouse line deficient for this regulatory candidate sequence within the 3'UTR of the TWEAK gene. According to our in vitro experiments, we expect increased baseline and inducible TWEAK levels and increased predisposition to TWEAK-dependent acute and inflammatory syndromes, i.e. CNT, nephritis, hepatitis, colitis.

Conclusions

In summary, we demonstrate TWEAK is post-transcriptionally regulated via an AU-rich element within the 3'UTR. Current research focuses on breeding and extensive phenotyping of the ΔARE2-strain in the context of CNT and other TWEAK-dependent disease models.

P 7

Effects of dietary potassium intake on progression of chronic kidney disease (NCCR project)

Valerie Olivier 1, Eric Feraille 1

1. Department PHYME Service of Nephrology University Medical center, Geneva, Switzerland

Background

Dietary treatment is seminal for the complex and challenging management of chronic kidney disease (CKD). There is no precise recommendation of daily potassium intake for the CKD patients except for hypertensive patients at CKD stage 1-2 and for CKD patients at advanced stages. The aim of the project was to assess the effects of potassium intake on the progression of CKD, using mouse models of kidney fibrosis.

Methods

We used 3 different mouse models of CKD to compare the effects of 3 different potassium diets on the progression of the kidney fibrosis: the unilateral ureteral obstruction (UUO) as an obstructive model, the POD-ATTAC mouse as a glomerular model, and the Pax8-DTR mouse as a tubular model. The POD—ATTAC mouse model displays a podocyte-specific apoptosis after the administration of a chemical inducer. The Pax8-DTR mouse model displays an apoptosis of the tubular cells after the injection of the diphteria toxin.

Results

In UUO, POD-ATTAC and DTR mice, high potassium intake induced higher fibrosis quantified by Sirius red staining of kidney slices (Fig.1). High potassium diet increased the abundance of the extracellular matrix protein fibronectin and decreased the expression levels of the epithelial marker Na-K ATPase. In association with high sodium intake, high potassium intake increased mRNA levels of inflammatory cytokines. In POD-ATTAC and Pax8-DTR mice, high potassium intake was also associated with lower glomerular filtration rate. Neither tubular cell apoptosis nor the hypoxia-sensitive HIF pathway were altered by dietary potassium.

Conclusions

High potassium intake induces more fibrosis leading to decreased kidney function in 3 models of mouse models of CKD. Reducing potassium intake should be taken into consideration as a way to slowdown CKD in future clinical trials.

P 8

Deletion of the sodium/hydrogen exchanger isoform 6 in mice is associated with an age-dependent loss of bone volume (NCCR project)

Daniela Hanke 1, Giuseppe Albano 1, Manuel Anderegg 1, Daniel Fuster 1

1. Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern and Department for BioMedical Research, University of Bern, Switzerland

Background

The sodium/hydrogen exchanger isoform 6 (NHE6) localizes to recycling endosomes, where it mediates endosomal alkalinization through K+/H+ exchange. NHE6 function in the endosome is essential for clathrin-mediated endocytosis, receptor recycling and endosomal signaling. Mutations in the SLC9A6 gene encoding the NHE6 isoform cause severe X-linked mental retardation, epilepsy, autism and corticobasal degeneration in humans.

Patients with SLC9A6 mutations exhibit skeletal malformations, and a previous study suggested a role of NHE6 in osteoblast-mediated mineralization.

Methods

NHE6 expression, osteoclast differentiation and cell-mediated resorption were assessed in osteoclast precursor cells isolated from wild-type and NHE6 knock-out mice. In a next series of experiments, we used primary osteoblasts, extracted from calvaria of new-born mice, to study NHE6 expression, proliferation, and cell-mediated mineralization. To determine the impact of these in vitro findings on structural bone parameters, we performed high-resolution microcomputed tomography (µCT) on lumbar vertebrae of wild-type and NHE6 knock-out mice.

Results

NHE6 transcript and protein are expressed in both primary osteoclasts and mineralizing osteoblasts. In vitro studies with osteoclasts and osteoblasts from NHE6 knock-out mice demonstrated normal osteoclast differentiation and osteoblast proliferation. However, NHE6-deficient osteoclasts exhibited a resorptive deficit, and the mineralization capacity was increased in osteoblasts lacking NHE6. Microcomputed tomography studies revealed a reduced bone volume at a single lumbar vertebral site (L4) but otherwise unaltered structural bone parameters in NHE6 knock-out compared to wild-type mice at 3 months of age. At 6 months of age, NHE6 knockout mice displayed a significantly reduced bone volume and trabecular number and increased trabecular space at all lumbar vertebrae studied (L3-L5) compared to wild-type.

Conclusions

Thus, loss of NHE6 results in an age-dependent loss of bone volume in mice. The results of our in vitro studies argue against a direct bone cell-autonomous cause of the bone phenotype observed in NHE6 knock-out mice and suggest extraosseus factors as likely mediators.

P 9

FGF23/FGFR signaling modulator MEMO binds and oxidizes ARHGDIA/Rho-GDP dissociation inhibitor 1 (NCCR project) *

Katalin Bartos 1, Sophie Braga 2, Olivier Bonny 3, Matthias Moor 1

1. Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern and Department for BioMedical Research, University of Bern, Switzerland 2. Department for BioMedical Research, University of Bern, Switzerland 3. Service of Nephrology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Background

Redox protein MEMO modulates receptor tyrosine kinase signaling by unknown mechanisms (Meira et al., Nat Cell Biol 2004; MacDonald et al., Science Signal 2014). *Memo1* deletion causes a phenotype partially resembling *Klotho* and *Fgf23*-deficient mice (Hänzi et al., FASEB J 2014; Moor et al., JBMR Plus 2018) and increases renal abundance of Rho-GTPase RhoA but prevents FGF23-dependent renal ERK phosphorylation and Rho-GTPase Rac1 activation (unpublished). Here, we investigated the potential interaction between MEMO and Rho-GTPase chaperone protein ARHGDIA/Rho-GDP dissociation inhibitor 1 and established a cellular model to investigate mechanisms of FGF23 signaling under *Memo1* deficiency.

Methods

Recombinant MEMO was pre-incubated with co-enzyme Cu2+ as CuCl2 followed by dialysis removal of free Cu2+. Recombinant ARHGDIA was incubated with H2O2, Cu2+-loaded MEMO, Cu2+-free MEMO or vehicle. Cysteine-reactive iodoacetyl tandem mass tag labelling and liquid chromatography tandem mass spectrometry (LC-MS/MS) was used to quantify reversible cysteine oxidation. Hyperoxidation was assessed by quantifying dioxidized and trioxidized Cys79 in ARHGDIA peptide matches. In HEK293 cells, Memo and ARHGDIA were overexpressed for immunoprecipitation. HEK293 cells stably overexpressing Klotho were treated with FGF23 to determine ERK phosphorylation and Egr1 abundance. By single and double-gRNA Approach, *Memo1* locus was targeted by CRISPR-Cas9 in HEK293-Klotho cells.

Results

Cu2+-loaded MEMO caused both reversible oxidation and irreversible trioxidation to sulfonate residues at ARHGDIA Cys79 in cell-free conditions, while H2O2 served as a positive control. MEMO and ARHGDIA proteins associated *in vitro* in HEK293 cells by immunoprecipitation. HEK293-Klotho cells were responsive to FGF23 in contrast to Klotho-nonexpressing cells. In HEK293-Klotho cells, CRISPR-Cas9 targeting *Memo1*exons 1 or 2 led to a significant decrease of *Memo1* expression in preliminary analyses.

Conclusions

Redox protein MEMO both associates and functionally interacts with ARHGDIA by oxidation of Cys79. HEK293- Klotho cells are a suitable experimental model to determine effects of *Memo1* deficiency on FGF23-FGFRRhoGTPase signaling.

* *Student paper*

POSTER PRESENTATIONS – TRANSPLANTATION

P 10

Designing T cells resistant to calcineurin inhibitors for cellular immunotherapies

Emmanuelle Landmann [1], Marianne Doelz [2], Lukas Jeker [1]

1. University of Basel, Department of Biomedicine, Basel, Switzerland & University Hospital Basel, Clinic for Transplantation Immunology and Nephrology, Basel, Switzerland , 2. University of Basel, Department of Biomedicine, Basel, Switzerland

Background

Genetically engineered cell-based therapies are rapidly evolving in medicine and have reached unprecedented clinical success rates in selected hematological malignancies. In solid-organ transplantation adoptive transfer of regulatory T cells are promising candidates to constrain alloimmune responses and reduce the need for nonspecific immunosuppressive drugs (IS). In patients still depending on IS, however, transferred cells are likely to be inhibited by the pharmaceuticals. Recently, our lab has elucidated the role of the microRNA cluster miR- 17-92 in T cell activation and showed that it promotes numerous gene networks, including the calcineurin- NFAT pathway (Dölz et al., unpublished results). Interestingly, mouse T cells that overexpress miR-17-92 are resistant to the well-established IS calcineurin inhibitors (CNI). This newly identified resistance mechanism harbors potential for adoptive T cell therapy in patients relying on IS. Therefore, we aim to genetically engineer human T cells to overexpress miR-17-92 to induce CNI resistance.

Methods

Primary T cells of healthy volunteers are isolated, and with the novel CRISPR/Cas9 technology the miR-17-92 transgene is safely integrated into the genome allowing constitutive expression of the microRNA. The engineered cells are then activated in the presence of CNI*in vitro*, and their activation status, proliferative capacity and cytokine expression are assessed by flow cytometry and compared to non-edited cells. Aiming for a clinical application, the primary T cells are also engineered on the GMP-compliant cell processing system CliniMACS Prodigy.

Results

We have established protocols for non-viral knock-in of human T cells. We are able to successfully integrate surrogate gene constructs of 3kb length in up to 25% of all T cells. This efficiency should be sufficient to engineer the microRNA overexpression constructs.

Conclusions

Our approach to protect therapeutic T cells from pharmaceutical inhibition of CNIs harbors potential for future cell-based immunotherapies, not only in solid-organ transplantation, but also in other disease states such as Graft-versus-host disease.

P 11

Development of an immunogenicity score for HLA-DQ eplets

Lara Schawalder [1], Gideon Hönger [1], Stefan Schaub [2]

1. Universitätsspital Basel, Basel, Switzrland 2. Clinic for Nephrology and Transplantation Immunology University Hospital Basel, Basel, Switzerland

Background

Eplets are defined as distinct amino acid configurations on the surface of HLA molecules. Many de novo HLA antibodies after kidney transplantation are directed against HLA-DQ, and several studies suggest that the HLADQ eplet mismatch load (= number of mismatched epelts) correlates with their development. However, each individual eplet might have a different immunogenicity, but this has not been explored in detail yet. The aim of this study was to estimate the immunogenicity of HLA-DQ eplets in a cohort of 221 pregnancies with HLA-DQ mismatches.

Methods

We defined the immunogenicity of an eplet by the frequency of antibody responses against it. Around 90% of all listed DQB1 or DQA1 eplets were at least 5 times mismatched and thus included for the calculation of their immunogenicity.

Results

The DQB1 eplets with the five highest immunogenicity scores were 55PP, 52PR, 52PQ, 85VG and 45EV; 25% percent of all DQB1 eplets were not reacting. The DQA1 eplets with the five highest immunogenicity scores were 25YS, 47QL, 55RR, 187T, and 18S; 17% percent of all DQA1 eplets were not reacting. The immunogenicity score had a slightly higher AUC to predict development of child-specific antibodies than various molecular mismatch scores (e.g. eplet mismatch load, amino acid mismatch load). Overlapping eplets were identified as a barrier to unambiguously assign the immunogenicity score based on HLA antibody reaction patterns.

Conclusions

In this conceptual study, we explored the immunogenicity of HLA-DQ eplets and created a map of potentially immunogenic regions on HLA-DQ molecules, which requires validation in clinical transplant cohorts. If confirmed, the immunogenicity score can help to distinguish between low and high immunogenic HLA-DQ mismatches. This information could be useful for individual patient management.

P 12

Outcome of patients who refuse to accept a kidney offer – single center observational study from 31 cases *

Alexander Born [1], Anita Hurni [1], Lucienne Christen [1], Franz Immer [2], Daniel Sidler [3]

1. Inselspital, Bern University Hospital, University of Bern, Department of Nephrology and Hypertension, Bern, Switzerland 2. Swisstransplant, the Swiss National Foundation for Organ Donation and Transplantation, Bern, Switzerland 3. Inselspistal, Bern, Switzerland

Background

Given the scarcy of donor kidneys eligible for transplantation, waitlisted patients generally accept kidney offers. In rare situations, candidates cannot be reached in time or kidney offers are turned down by the patient. Here we evaluated the frequency and outcome of turned down kidney offers.

Methods

We screened allocation justifications for reasons suggestive for a decline by the patient. Among 15815 kidney offers from 1541 donors from 11.07.07 through 29.11.2019, 2040 involved candidates waitlisted at the University of Bern. Outcome of patients who declined offers were compare to patients who accepted their first kidney offer. The consequence of declines on the allocation process and cold ischemia time was measured and compared. Finally, the outcome in respect of transplant fate and survival was measured.

Results

Among the 2040 allocations, 322 kidneys were transplanted and in 31 instances, candidates declined an offer or were not contactable within meaningful time. Baseline characteristics, marital status, work capacity and income were similar among both groups. Patients who refused allocations tended to have a higher work capacity, lower income and live in a single household. For the orphaned kidney, the allcoation process and cold ischemia time was insignificantly longer. After decline, 80% patients subsequently received a transplantation with an additional median waiting time of 6 months. After sucessful transplantation, failure-free survival was comparable to paitents who accepted their first organ offer.

Conclusions

We here demonstrate a small, yet comprehensive and well characterized cohort of transplant candidates that refuse to accept an organ offer. Outcome is good, although some 20% of patients will not receive a kidney transplantation within the next two years. Declines of organ offers substantially increases total active waiting time. Refusal of an organ offer prolongs the allocation process and potentially cold ischemia time for the orphaned kidney, although larger cohorts are needed to verify this data.

** Student paper*

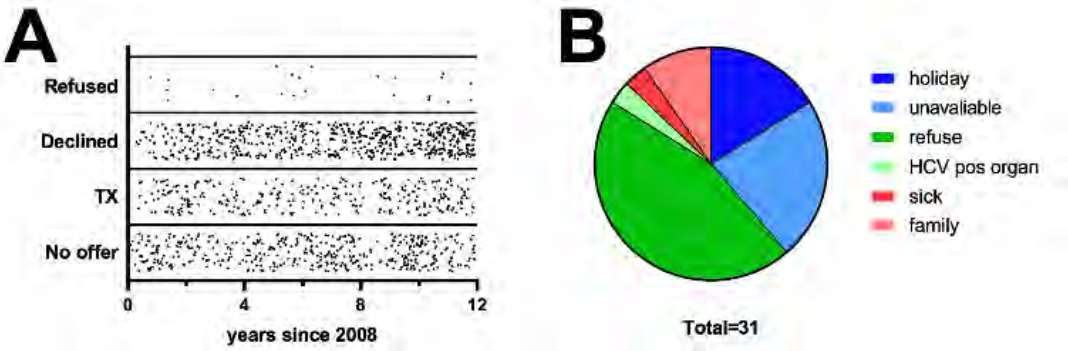


Figure 1: Allocation decisions at the University Hospital Bern for 2042 deceased donor evaluations in Switzerland from 5.1.2008 through 05.12.2019. (A) Treatment decisions over time, each dot represents an evaluated donor. (B) Justifications of organ refusal by patients.

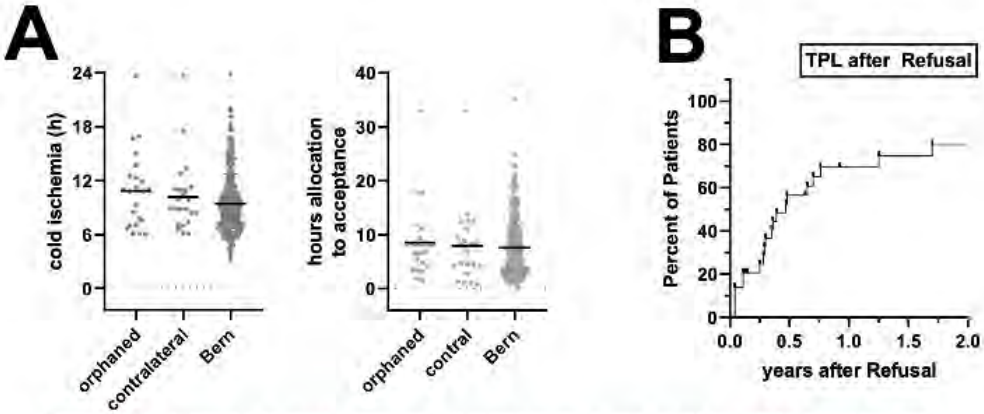


Figure 2: (A) Time differences in the allocation process and cold ischemia between an organ refused by a potential recipient (orphaned n=24), compared to the contralateral kidney (n=24) and controll group where the first recipiant accepted the organ offered(n=251). (B) Time from refusal of an offer untill another organ was offered and successfully transplanted.

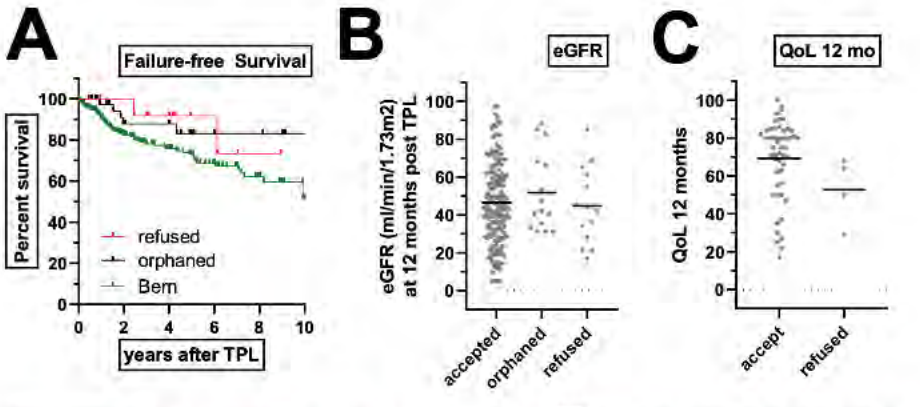


Figure 4: Outcomes of the 293 transplanted patients at the University Hospital of Bern, comparing patients accepting the first offered organ, to those trefused and those, accepting the orphaned kidney. (A) Failure-free graft survival over time in years. (B) eGFR after 12 months. (C) Quality of life after 12 months.

P 13

50 Years Functioning Renal Graft Performed in Childhood

Ernst Leumann [1], Karine Hadaya [2], Luc Paunier [3], Eric Girardin [4], Giuseppina Spartà [1]

1. Univ. Children's Hospital Zurich, Zurich, Switzerland 2. Division of Nephrology, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland 3. Department of Pediatrics, Geneva University Hospital, Geneva, Switzerland 4. Pediatric Nephrology Unit, Department of Pediatrics, Geneva University Hospital, Geneva, Switzerland

Background

In 1970, there was widespread consensus that only patients aged 15 to 50 years should be offered renal replacement therapy. However, first results of renal transplantation in younger patients performed in the United States had shown promising results.

Methods

The propositus, a 7 y/o boy with ESRF due to HUS, was treated in 1970 for 4 months by peritoneal dialysis at the Dept. of Pediatrics of the University Hospital in Geneva and was then transferred to the Univ. Children's Hospital in Zurich for renal transplantation. After 4 months of haemodialysis (weekly 3 times 4 hours with a small Gambro plate) the patient underwent renal transplantation from a deceased adult donor on Dec. 15, 1970, performed by the late F. Largiadèr. Immuno-suppression was based on methylprednisolone then prednisone and azathioprine (3 mg/kg/d).

Results

The boy had 2 biological mild rejection episodes at 2 and 5 weeks controlled by increased doses of steroids. During the first year he developed severe Cushing syndrome that disappeared following switching after 8 months from daily to alternate day administration of prednisone. The boy went to regular school and had a normal adult life. Major side effects are severe skin lesions due to azathioprine. At last visit in August 2020 he was well, height 168 cm, weight 55 kg, serum creatinine 138 µmol/l, eGFR 49 ml/min/1.73 m^2. No hypertension, no lipid abnormalities, no diabetes. Immunosuppression still consists of prednisone (20 mg/48h) and azathioprine (62.5 mg/day).

Conclusions

Kidney transplantation in paediatric patients had only very rarely been done in Europe in 1970.

To the best of our knowledge, we report hereby the longest functioning kidney transplant from a deceased donor worldwide performed in a child. We speculate that renal function was maintained because the patient never received calcineurin inhibitors.

P 14

Combining Letermovir with Valganciclovir May Allow an Early Switch From Foscarnet Among Kidney-Transplant-Recipients With Ganciclovir-resistant CMV Infection

Elena Rho [1], Bettina Naef [1], Rudolf Wüthrich [1], Thomas Müller [1], Thomas Schachtner [1], Seraina Von Moos [1]

1. University Hospital of Zurich, Zurich, Switzerland

Background

Ganciclovir (GCV) resistant cytomegalovirus (CMV) infection is a concerning condition in solid organ transplantation. Since treatment with foscarnet (FOS) is associated with nephrotoxicity, alternative treatments are required. Oral letermovir (LTV) might be a less toxic option. It has been approved for CMV prophylaxis, but its efficacy in treating active CMV infection is unclear.

Methods

In this retrospective, single-centre study, all kidney transplant recipients (KTR) between 2009 and 2019 who developed GCV-resistant CMV infection were included. CMV viral loads, kidney function and patient outcome were compared between two treatment regimens: FOS ± switch to valganciclovir (VGCV) (standard, ST) versus FOS + switch to LTV ± VGCV (novel, NOV). The switch was done once viral loads were <2'000 IU/ml.

Results

In our cohort 17% (133/793) of KTR were at high risk for CMV infection. A total of 14 patients (1.7%) had a proven GCV resistance, of which 10 patients were treated by ST and 4 by NOV regimen. Total duration of FOS (median 48 days ST vs 27 days NOV) showed a moderate correlation with deterioration of kidney function ($r = 0.34$, $p = 0.2$). In the ST group, 56% had a relapse of CMV viremia >10.000 IU/ml after switch to oral treatment as compared to 25% in the NOV group. Patient survival was 50% in the ST versus 100% in the NOV treatment group.

Conclusions

Our results suggest that a switch from FOS to oral VGCV+LTV may be safe and efficacious in controlling CMV infection with less nephrotoxicity and improved patient outcome.

P 15

Establishing and comparing two methods for donor-derived cfdna quantification in urine and plasma from kidney transplant recipients

Nicholas Küng [1], Severine Arcioni [1], Christian Kuhn [2], Katharina Staufer [3], Vanessa Banz [3], Carlo Largiader [1], Daniel Sidler [4], Ursula Amstutz [1]

1. University Institute of Clinical Chemistry, Inselspital Bern University Hospital, University of Bern, Bern, Switzerland 2. Klinik für Nephrologie und Hypertonie, Inselspital, Bern, Switzerland 3. Department of Visceral Surgery and Medicine, Inselspital Bern University Hospital, University of Bern, Bern, Switzerland 4. Inselspital, Bern University Hospital, University of Bern, Department of Nephrology and Hypertension, Bern, Switzerland

Background

In allograft monitoring of solid organ transplant recipients, there is an unmet need for diagnostic methods that are less invasive than tissue biopsies. In this context, liquid biopsy has emerged as a novel approach using quantification of donor-derived cell-free DNA (dd-cfDNA) in body fluids.

Methods

Two approaches were compared for dd-cfDNA quantification in urine and plasma of kidney recipients: droplet digital PCR (ddPCR) with allele-specific detection of seven *HLA-DRB1*alleles and the Y chromosome, and highthroughput sequencing (HTS) with a QIAseq custom targeted DNA panel incorporating Unique Molecular Identifiers (UMI) targeting 117 common, disease-unrelated SNPs. Dd-cfDNA was quantified as donor copies, utilizing UMI information for HTS, as well as fractional abundance (FA).

Results

In 44 plasma samples from stable recipients analyzed by ddPCR, the median donor copies/ml was 3.17 (IQR: 1.4-8.47) with a median FA of 0.22% (0.11-0.47%). For 25 creatinine-normalized urine samples from the same patients the median donor copies/µmol creatinine was 20.2 (7.1-41.3) with a median FA of 44% (4.1-68.4%). In 25 urine samples, strong correlations for total cfDNA copies ($R = 0.95$, $p < 10^{-5}$), FA ($R = 0.97$, $p < 10^{-7}$) as well as for donor copies ($R = 0.87$, $p < 10^{-5}$) was observed between ddPCR and HTS. In samples from 19 newly transplanted recipients, the FA <24 hours after surgery was 62.91% (21-85%) for urine and 5.13% (2.4-11%) for plasma, and decreased to 23.2% (9.1-35%) and 0.55% (0.30-0.93%), respectively after 3-5 days.

Conclusions

This first direct comparison of dd-cfDNA in urine and plasma from stable kidney recipients revealed overall higher quantities of dd-cfDNA urine, but with a highly variable FA, highlighting the importance of absolute dd-cfDNA quantification in urine. The strong correlation with ddPCR indicates the suitability of this new HTS method both for relative and absolute dd-cfDNA quantification, enabling further evaluation of its potential for minimally-invasive allograft monitoring.

P 16

Preservation of kidney function in kidney transplant recipients by alkali therapy (Preserve-Transplant Study)

Alexander Ritter [1], Anna Wiegand [1], Nicole Graf [2], Suzan Dahdal [3], Spyridon Arampatzis [3], Daniel Sidler [3], Karine Hadaya [4], Thomas Müller [1], Carsten Wagner [5], Rudolf Wüthrich [1], Nilufar Mohebbi [1]

1. Universitätsspital Zürich, Klinik für Nephrologie, Zürich, Switzerland 2. Graf Biostatistics, Winterthur, Switzerland 3. Inselspital, Bern University Hospital, University of Bern, Department of Nephrology and Hypertension, Bern, Switzerland 4. Division of Nephrology, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland 5. Institute of Physiology, University of Zurich, Zurich, Switzerland

Background

Kidney transplantation is the treatment of choice for patients with ESRD. Short- and long-term graft survival after kidney transplantation have sig-

nificantly improved within the last decades but declining transplant function or even graft loss is still a common issue. Metabolic acidosis (MA) is highly prevalent in kidney transplant recipients (KTRs) and several recent observational studies have shown that MA may be a significant risk factor for graft loss and mortality. However, randomized data on the role of alkali treatment on allograft function is lacking. An alkali treatment study in KTRs is of high importance and has the potential to show that such treatment may reduce the progression towards graft failure.

Methods

This study is a multi-center, prospective, randomized, single-blinded, placebo-controlled interventional trial to test the superiority of alkali treatment in comparison to placebo for preservation of kidney function in 240 kidney transplant recipients. The individual duration of the study is two years. The patients are randomized into two arms: intervention arm (sodium hydrogen carbonate) and placebo arm. The study is supported by the Swiss National Science Foundation as an investigator-initiated clinical trial.

Results

Patient recruitment has started on June 12th, 2017. By the end of the recruitment phase on July 14th, 2019, 243 patients had been randomized. In the preliminary baseline data (mean (sd)) patient age is 56.0 (13.4) years, eGFR (CKD-EPI) 47.8 (16.0) ml/min/1.73 m^2 and serum bicarbonate level 21.1 (2.7) mmol/l. 69.7 percent of study participants are male. So far, the study medication is tolerated well.

Conclusions

The Preserve-Transplant Study has been launched successfully and the recruitment goal of 240 patients was achieved. The results of the Preserve-Transplant Study will have an impact on the treatment of MA in kidney transplant patients.

P 17

Benefits of swallowing bitter pills - early esophagus cancer revealed by large capsules in an alkali treatment trial

Alexander Ritter 1, Nilufar Mohebbi 2, Ove Carstens 3, Daniel Sidler 4

1. *Universitätsspital Zürich, Klinik für Nephrologie, Zürich, Switzerland* ***2.*** *Universitätsspital Zürich, Klinik für die Nephrologie, Zürich, Switzerland* ***3.*** *Division of Visceral Surgery and Medicine, Inselspital Bern, Bern, Switzerland* ***4.*** *Inselspital, Bern University Hospital, University of Bern, Department of Nephrology and Hypertension, Bern, Switzerland*

Background

Metabolic acidosis (MA) in kidney transplant recipients is highly prevalent. Given that bicarbonate has a relatively high blood concentration, often a large number of capsules of alkali supplements are needed to increase the serum bicarbonate concentration appropriately. Consequently, the pill burden is a major concern of many patients.

Methods

We report a clinical case of a 73-year-old male patient with a history of heart and deceased kidney transplantation suffering from chronic MA, who was enrolled in the Preserve-Transplant Study. This multicenter randomized, placebo-controlled trial investigates the impact of 24 months of alkali treatment on glomerular filtration rate in kidney transplant patients with MA. The study medication was titrated to a dose of three capsules of 500 mg sodium bicarbonate daily.

Results

The patient complained about difficulties in swallowing the study medication with odynophagia and regurgitation. Consequently, he considered quitting the trial participation. Gastroscopy revealed an early substenosing esophagus carcinoma and combined chemo- and radiotherapy were planned as curative treatment.

Conclusions

Difficulties in swallowing large capsules, such as sodium bicarbonate preparations, warrant further work-up to exclude as in this case other underlying medical problems. Some investigators differentiate between off-target tissue effects (i.e. action on correct drug-target, yet in untargeted tissue or organ) and off-target protein effects (i.e. action on untargeted molecules). This example demonstrates an off-target effect of sodium bicarbonate supplementation deriving from the morphological features of its capsule and not its biochemical properties - namely subtotal esophageal occlusion due to the concomitant esophageal cancer. Consequently, the effect of verum and placebo in the study would have likely been the same. Some studies, not all, demonstrated a beneficial effect of trial participation on outcomes. In our case the consequent study drug administration and thorough study visits likely led to an earlier diagnosis of the esophagus cancer and a potentially curative treatment.

P 18

Self-perceived awareness, preventive measures and general health of kidney transplant recipients during the SARS-CoV-2 Pandemic - A prospective single center observational study *

Nathalie Barandun 1, Laura N. Walti 2, Daniel Sidler 3

1. *Medical Faculty, University Bern, Bern, Switzerland* ***2.*** *Department of Infectious Diseases, University Hospital Insel Bern, Bern, Switzerland* ***3.*** *Inselspital, Bern, Switzerland*

Background

The current SARS-CoV-2 pandemic has a major impact on awareness for and prevention of infections in general, but notably in patients at elevated risk for severe COVID-19. Kidney transplant recipients (KTR) are considered high risk candidates due to systemic immunosuppression and high prevalence of co-morbidities, including hypertension, impaired renal function, vascular disease, diabetes mellitus and obesity.

Methods

We assessed self-reported awareness, preventive measures and general health perception in 92 KTR before and after the first wave of the SARS-CoV-2 pandemic. Baseline evaluation was performed in October 2019 for an unrelated project on opportunistic infections after kidney transplantation. A follow-up with additional COVID-19 related questions was performed in May 2020.

Results

In our cohort, 100% of patients were considered at substantial risk for severe COVID-19 courses due to immunosuppressive treatment, additionally 82% had eGFR <60 ml/min/1.73 m^2, 79% hypertension, 15% vascular disease (CAD, CVD, PAVK) and 20% obesity with BMI >30 kg/m^2. During the pandemic, 75% lived in a household with at least one additional family member, among those 14% with children. 33% of patients were employed, among those all took measures of social distancing (home office, leave sick). Self-reported health perception did not change between October 2019 and May 2020. 25% of patients reported a lower self-perceived incidence of infections during/after the COVID-19 lock-down; 48% at least once unspecific symptoms, among those 38% suffered from fatigue, 22% from reduced general health or 22% from other unspecific symptoms. During the period investigated, none of the patients was diagnosed with SARS-CoV-2 infection.

Conclusions

Among high-risk individuals, such as KRT, awareness for social distancing was high. Self-perceived health was equivalent before and during/after the SARS-CoV-2 pandemic. Incidence of COVID-19 was negligible. Interestingly, patients reported a high frequency of manifestations compatible with viral symptoms; this could impact clinical management in the upcoming winter.

** Student paper*

POSTER PRESENTATIONS – CLINICAL NEPHROLOGY / HYPERTENSION / MINERAL / ELECTROLYTES

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Acute Kidney Injury in Patients with COVID-19

Matthias Diebold 1, Stefan Schaub 1, Emmanuelle Landmann 1, Juerg Steiger 2, Michael Dickenmann 1

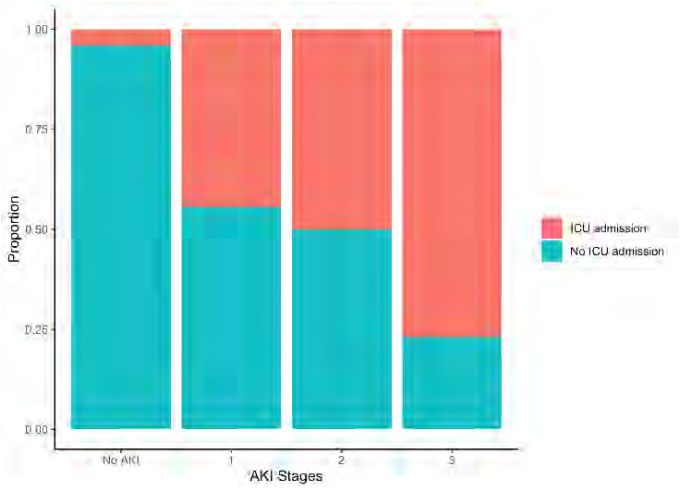
1. Clinic for Nephrology and Transplantation Immunology University Hospital Basel, Basel, Switzerland 2. Universitätsspital Basel, Transplantationsimmunologie und Nephrologie, Basel, Switzerland

Background

Data remains scarce about acute kidney injury (AKI) and patients with corona virus disease-2019 (COVID-19). We examined characteristics, presentation and risk factors of AKI in patients hospitalized with COVID-19.

Methods

We reviewed health records of patients hospitalized with a positive nasopharyngeal polymerase chain reaction test for SARS-COV2 between February 01, and June 30, 2020, at the University Hospital of Basel. The nadir creatinine of the hospitalization was used as baseline. AKI was defined according to the KDIGO guidelines as a 1.5x increase of baseline creatinine and renal recovery as a discharge creatinine<1.25x baseline creatinine. Least absolute shrinkage and selection operator(LASSO) regression was performed to select predictive variables of AKI. Based on this a final model was chosen.



Results

Of 188 patients with COVID-19, 41(22%) developed AKI, and 11(6%) required renal replacement therapy(RRT). Patients with AKI were older with higher white blood cell count and c-reactive protein levels(Table1). AKI developed after a median of 10 days(interquartile range[IQR] 5-13) since the first symptoms and a median of 1 day(IQR 0-5) after hospital admission. The peak AKI stages were stage 1 in 44%, stage 2 in 24% and stage 3 in 32%. Renal recovery at discharge was observed in 61% of all AKI episodes. Of patients requiring RRT 5(45%) patients died and 1(9%) was still on dialysis at discharge. Overall mortality was 10% and in patients with AKI 27%. Urine microscopy was available in 16(39%) patients with AKI and predominantly(70%) indicated acute tubular injury. Age(adjusted Odds ratio[aOR] 1.04, 95%CI 1.01-1.08;p = 0.024), history of chronic kidney disease(aOR 3.47, 95%CI 1.16-10.49;p = 0.026), c-reactive protein levels(aOR 1.01, 95%CI 1.00-1.02;p = 0.002) and creatinine kinase(aOR 1.00, 95%CI 1.00-1.01;p = 0.002) were associated with development of AKI.

Conclusions

AKI is common but mostly reversible in hospitalized patients with COVID-19. It is more often seen in patients with severe COVID-19 illness and likely induced by acute tubular injury.

Variable	Overall (n = 188)	No AKI (n = 147)	AKI (n = 41)	p-Value
Demographics				
Age (years)	62 [48, 73]	59 [46, 72]	67 [60, 77]	0.002
Male (%)	115 (61)	83 (56)	32 (78)	0.018
Medical history				
CKD (%)	28 (15)	13 (9)	15 (37)	<0.001
Hypertension (%)	86 (46)	59 (40)	27 (66)	0.004
Diabetes (%)	35 (19)	25 (17)	10 (24)	0.363
Chronic heart failure (%)	12 (6)	7 (5)	5 (12)	0.139
COPD/Asthma (%)	23 (12)	17 (12)	6 (15)	0.595
Active Cancer	14 (7)	12 (8)	2 (5)	0.738
Coronary artery disease (%)	27 (14)	18 (12)	9 (22)	0.133
Peripheral artery disease	5 (3)	2 (1)	3 (7)	0.070
BMI[a] (kg/m^2)	28.0 [24.8, 31.0]	27.0 [24.0, 30.2]	30.5 [28.5, 33.2]	0.020
Laboratory parameters at admission				
Hemoglobin (g/l)	135 [124, 147]	136.0 [125, 147]	132 [120, 145]	0.551
White blood cell count (10^9/l)	6.1 [4.5, 8.3]	6.0 [4.3, 7.6]	7.7 [5.3, 10.1]	0.004
Lymphocyte count (10^9/l)	1.0 [0.7, 1.4]	1.1 [0.8, 1.4]	0.6 [0.4, 1.1]	<0.001
Platelet count (10^9/l)	210 [159, 277]	215 [172, 277]	178 [136, 276]	0.120
C-reactive protein (mg/l)	43 [16, 103]	35 [12, 72]	104 [48, 163]	<0.001
D-dimer[b] (mg/l)	0.7 [0.4, 1.6]	0.6 [0.4, 1.2]	1.2 [0.5, 4.2]	0.012
Lactate dehydrogenase (U/l)	295 [222, 408]	265 [208, 360]	395 [283, 485]	<0.001
Creatinine kinase U/l)	97 [60, 198]	85 [53, 139]	212 [130, 434]	<0.001
Sodium (mmol/l)	136 [133, 139]	136 [133, 139]	136 [133, 139]	0.634
Potassium (mmol/l)	3.9 [3.6, 4.2]	3.9 [3.6, 4.1]	4.1 [3.8, 4.8]	0.009
Serum creatinine (mmol/l)	78 [63, 98]	74 [61, 89]	121 [78, 201]	<0.001
Blood urea nitrogen (mmol/l)	5.2 [3.8, 7.3]	4.7 [3.5, 6.1]	8.7 [5.7, 15.3]	<0.001
Preadmission medication				
Angiotensin-converting enzyme inhibor (%)	29 (15)	23 (16)	6 (15)	1.000
Angiotensin II receptor blocker (%)	47 (25)	30 (20)	17 (41)	0.008
Loop diuretic (%)	17 (9)	13 (9)	4 (10)	0.767
Thiazid (%)	22 (12)	14 (10)	8 (20)	0.098
Diuretics other (%)	3 (2)	0 (0)	3 (7)	0.010
Hospitalization				
Length of stay (days)	6 [4, 10]	6 [4, 8]	15 [7, 25]	<0.001

Table 1 Baseline Characteristics AKI denotes acute kidney injury; CKD denotes chronic kidney disease; COPD denotes chronic obstructive pulmonary disease; Values are numbers (percentages) or median [Interquantile range]; p-Value are calculated between no- AKI and AKI using a Mann–Whitney U-test for continuous variables and Fisher's exact test for categorical variables. a Missing in 60%, b Missing in 34%

P 20

Two phase 3, multicenter, randomized studies of intermittent oral roxadustat in anemic CKD patients on (PYRENEES) and not on (ALPS) dialysis

Ciro Esposito 1, Botond Csiky 2, Avtandil Tataradze 3, Michael Reusch 4, Cong Han 5, Wladyslaw Sulowicz 6

1. Department of Internal Medicine and Medical Therapy, Unit of Nephrology and Dialysis, ICS Maugeri SpA - SB, University of Pavia, Italy 2. Department of Medicine and Nephrology-Diabetes Center ,FMC Dialysis Center, Hungary 3. Dialysis, Nephrology and Transplantation Union of Georgia, National Center of Urology, Georgia 4. Development Medical Science, Astellas Pharma Europe B.V. United Kingdom 5. Biostatistics, Astellas Pharma, Inc. The United States 6. Department of Nephrology, Jagiellonian University, Poland

Background

Roxadustat is an oral HIF-PHI in development for treatment of CKD anemia.

Methods

Two phase 3 European studies enrolled non–dialysis-dependent (NDD; ALPS) and dialysis-dependent (DD; PYRENEES) patients with CKD anemia. In the double-blind NDD study, patients with hemoglobin (Hb) ≤10 g/dL not treated with erythropoiesis-stimulating agents (ESAs) were randomized (2:1) to roxadustat or placebo for 52- 104 weeks. In the open-label DD study, patients with Hb 9.5-12 g/dL treated with ESAs were randomized (1:1) to roxadustat or ESAs for 52-104 weeks. Primary endpoints were change of average Hb levels at Weeks 28-52 from baseline. Secondary endpoints included change of average low-density lipoprotein cholesterol (LDL) at Weeks 12-28 from baseline, time to use of rescue therapy (NDD), and mean monthly IV iron use through Week 36 (DD). Occurrence of adverse events (AEs) was also assessed.

Results

The NDD study randomized 594 patients (roxadustat, n = 391; placebo, n = 203); the DD study randomized 836 patients (roxadustat, n = 415; ESA, n = 421). Mean (SD) change of average Hb levels was 1.988 (0.953) for roxadustat and 0.406 (0.979) for placebo (P<0.001) in NDD and 0.396 (0.773) for roxadustat and 0.183 (0.860) for ESA in DD (P<0.001). The LS mean difference (95% CI) in LDL was -0.701 (-0.83, -0.57; P<0.001) mmol/L versus placebo (NDD) and -0.377 (-0.451, -0.304; P<0.001) mmol/L versus ESA (DD). In NDD, roxadustat was superior to placebo in time to use of rescue therapy (hazard ratio [95% CI], 0.238 [0.17, 0.33]; P<0.001). In DD, roxadustat was superior to ESA in mean monthly IV iron use (LS mean difference [95% CI], -31.9 [-41.4, -22.4]; P<0.001). Common Aes included: ESRD, hypertension, peripheral edema, and decreased GFR (NDD); hypertension, arteriovenous fistula thrombosis, headache, and diarrhea (DD).

Conclusions

Roxadustat was effective in achieving and maintaining Hb levels compared with placebo and ESA in NDD- and DD-CKD patients, respectively.

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Plasma markers of mineral metabolism in ADPKD patients treated with tolvaptan

Matteo Bargagli 1, Nasser A. Dhayat 2, Manuel Anderegg 2, Mariam Semmo 2, Uyen Huynh-Do 2, Bruno Vogt 2, Pietro Manuel Ferraro 1, Daniel G. Fuster 2

1. *U.O.C. Nefrologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Largo Agostino Gemelli 8, 00168, Roma, Italia* ***2.*** *Division of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 15, 3010, Bern, Switzerland*

Background

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by a unique bone and mineral phenotype. Patients affected by ADPKD show parathyroid hormone (PTH) resistance, a better-preserved cortical bone mass, higher sclerostin levels, lower bone turnover and total alkaline phosphatase compared to other chronic kidney disease (CKD) aetiologies. To date, the association between tolvaptan administration and serum biomarkers of mineral and bone disorder (CKD-MBD) has yet to be investigated.

Methods

We conducted an analysis of patients enrolled in the Bern ADPKD registry, a prospective observational cohort study. Serum parameters for CKD-MBD and 24-hour urine analyses were performed at baseline and then at yearly follow-ups. Multivariable linear regression models adjusted for age, sex, body mass index, eGFR, visit, time of follow-up and height-adjusted total kidney volume, were applied to study changes in serum parameters relevant for CKD-MBD between patients either treated or not treated with tolvaptan.

Results

A total of 125 participants (38 with and 87 without tolvaptan treatment) were included in the analysis. After adjusting for potential confounders, tolvaptan treatment was significantly associated with reduced plasma PTH concentration (β -50.14; 95%CI, -91.73 to -8.54; P = 0.019) and increasing plasma bicarbonate concentration (β 2.81; 95%CI, 1.24 to 4.39; P = 0.001) and ionized but not total plasma calcium (β 0.07; 95%CI, 0.02 to 0.13; P = 0.01 and β 0.12; 95%CI, -0.02 to 0.26; P = 0.089, respectively). No differences were found between groups at any time in serum phosphate, TmP/GFR, plasma fibroblast growth factor 23, plasma alkaline phosphatase, blood pH, 1,25(OH)2 and 25(OH) vitamin D.

Conclusions

We demonstrated that tolvaptan influences the ADPKD-specific bone and mineral metabolism. Tolvaptan administration seems to improve acid-base status, to reduce PTH-resistance and consequently increasing serum ionized calcium in ADPKD patients. Future prospective studies are needed to further assess its effect on bone mineral density and the risk of fractures.

P 22

Seasonal changes in ambient temperature have no significant association with eGFR in primary care patients in Switzerland

Stefan Zechman 1, Fabio Valeri 1, Maria Staudinger 2, Pietro Cippà 3, Jan Seibert 2, Simeon Schietzel 4, Oliver Senn 1, Harald Seeger 5

1. *Institute of Primary Care, University of Zurich, Zurich, Switzerland* ***2.*** *Department of Geography, University of Zurich, Switzerland ,* ***3.*** *Division of Nephrology, Ente Ospedaliero Cantonale, Lugano, Switzerland* ***4.*** *Division of Nephrology, University Hospital Bern, Bern, Switzerland* ***5.*** *Universitätsspital Zürich, Klinik für Nephrologie, Zürich, Switzerland*

Background

Clinically, it is well recognized that hypovolemia carries a significant risk of acute kidney injury. Therefore, nephron-protective counseling generally includes temporal suspension or reduction of diuretic and antihypertensive medication in circumstances of imminent fluid loss like diarrhea or increased perspiration. It is unclear whether ambient temperature significantly influences kidney function. We hypothesized, that there is an inverse correlation between ambient temperature and kidney function in a large primary care cohort from Switzerland. We further presumed that predefined subgroups such as individuals with older age, preexisting kidney disease, additional comorbidities, or those on therapy with renin-angiotensin system (RAS) blockers might show increased vulnerability during periods of increased ambient temperature with regard to deterioration of kidney function.

Methods

For this retrospective cross-sectional study, we analyzed data from primary care patients between 18 and 99 years of age, which were registered in the FIRE (Family medicine ICPC-Research using Electronic medical records) database.

Results

We included 18'000 primary care patients with at least 4 creatinine measurements each between 2009 and 2018. Total number of creatinine measurements was 132'176. Mean age of patients was 68.8 years (±14.8). Every temperature increase by 1°C (p <0.001) was associated with an eGFR decrease of 0.04 mL/min. In the multivariate regression, ambient temperature >30°C either on the day of creatinine measurement, or one or two days before, did not have a significant influence on average eGFR in the entire population or on predefined subsets of patients with presumed higher temperature vulnerability.

Conclusions

In Switzerland, ambient temperature even >30° C does not seem to have a relevant impact on eGFR in a primary care population.

P 23

Acute kidney injury in severe COVID-19: a single center experience

Nicola Beria 1, Jennifer Scotti Gerber 2, Giorgia Bianchi 1, Pietro Cippà 2

1. *Division of Nephrology, Ente Ospedaliero Cantonale, Locarno, Switzerland* ***2.*** *Division of Nephrology, Ente Ospedaliero Cantonale, Lugano, Switzerland*

Background

Acute kidney injury (AKI) is increasingly recognized as an important manifestation of severe COVID-19. We report our experience in patients admitted to the intensive care unit (ICU) of a dedicated COVID-19 hospital during the first COVID-19 wave in Ticino (Switzerland).

Methods

We retrospectively analyzed the cohort of patients admitted to the ICU of the Regional Hospital of Locarno from March 1stto May 31st, 2020.

Results

Among the 576 hospitalized COVID-19 patients, 88 were admitted to the ICU. Median age was 68 years, and 70% were male, 26% had chronic kidney disease stage 3 or higher (stage 3: 18%, stage 4-5: 8%), 54% had hypertension, 28% diabetes, 15% were smokers. AKI occurred in 66% (58/88) of the patients, with 25 patients having stage 1, 5 stage 2, and 28 stage 3 AKI, according to KDIGO-classification. Mortality was higher in patients with AKI as compared to patients without AKI (48% vs. 17%, p = 0.005). Mortality increased with severity of AKI: 38% in the AKI 1 group, 54% in AKI 2-3 (p value for trend = 0.02). Length of stay (LOS) was significantly longer in AKI compared to non-AKI patients (p = 0.028 for overall hospital LOS, p = 0.045 for ICU LOS). We did not find any difference among patients with and without AKI in terms of age, gender,

BMI, prevalence of CKD, or previous exposure to ACE inhibitors or angiotensin 2 receptor blockers.

Conclusions

AKI is a frequent manifestation of severe COVID-19 and is strongly associated with mortality.

P 24

Measured and estimated GFR in 1 the ICU: a prospective study

David Legouis [1], Frederic Sangla [1], Thomas Verrissimo [2], Sophie De Seigneux [2]

1. *Division of Intensive care, Geneva University Hospitals, Geneva, Switzerlad* ***2.*** *Division of Nephrology, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland*

Background

Estimation of renal function is usually not appropritae in the intensive care unit. Our aim in this study was to compare estimated glomerular filtration rate (GFR) using classical static and kinetic equations to measured GFR assessed by plasma iohexol clearance in a mixed population of critical care

Methods

We performed an Interventional prospective single center study in unselected patients older than 18 and admitted to a general intensive care unit. We measured GFR by the plasma clearance of an intravenous single dose of iohexol and used estimation of GFR with creatinine or cystatin C-based standard and kinetic equations as well as urinary creatinine clearance.

Results

63 patients were included with a median age of 66 years old. The median mGFR was 51 (IQR, 19-85) ml/min/1.73 m^2. All used equations displayed significant biases, high errors and poor accuracy when compared to mGFR, overestimating renal function. The highest accuracy and lowest error were observed with cystatin C based CKD-EPI equations. Both MDRD and Cockcroft-Gault equations displayed the lowest performance. Kinetic models did not improve performances,except in patients with unstable creatinine levels. Creatinine but not cystatin C based estimations largely derived over ICU stay, which appeared more related to sarcopenia than fluid balance. Finally, eGFR misclassified patients according to classical GFR categories in approximately half of the studied cases.

Conclusions

All known eGFR equations displayed high biases and unacceptable errors when compared to mGFR in a mixed ICU population, with the lowest performance related to creatinine-based equations compared to cystatin C. In the ICU, we advocate for caution when using creatinine based eGFR equations. Drifting of serum creatinine levels over time should also be taken into consideration when assessing renal function in the ICU.,

P 25

Safety of kidney biopsy when performed as an outpatient procedure

Harald Seeger [1], Marco Bonani [1], Nina Weber [2], Rudolf Wüthrich [3], Andreas Kistler [4]

1. *Universitätsspital Zürich, Klinik für Nephrologie, Zürich, Switzerland* ***2.*** *Institut für Nephrologie und Dialyse, Stadtspital Waid, Zürich, Switzerland* ***3.*** *Universitätsspital Zürich, Klinik für die Nephrologie, Zürich, Switzerland* ***4.*** *Cantonal Hospital Frauenfeld, Switzerland*

Background

Kidney biopsy remains the gold standard for the diagnosis of most renal diseases and kidney allograft dysfunction. A major obstacle to performing a kidney biopsy are safety concerns. Hence, there is interest in a precise estimate of the incidence of complications and their risk factors. Many safety measures are not evidence based, therefore biopsy practices vary widely between centers, e.g. with respect to post-procedure monitoring and whether kidney biopsies are performed as cost-effective outpatient procedures. We determined the rate and timing of kidney biopsy complications in our center, compared the complication rate between native and transplant kidney biopsies, evaluated the usefulness of a post-biopsy ultrasound before discharge and identified risk factors for complications.

Methods

We performed a single center, retrospective, observational study at the Division of Nephrology of the University Hospital Zurich including all patients (n = 1468) who underwent renal biopsy (n = 2239) between January 2005 and December 2017. Main outcomes were major bleeding (primary outcome) and any other bleeding or nonbleeding complications (secondary outcomes).

Results

Major bleeding was observed in 28/732 (3.8%) inpatient and in 15/1507 (1.0%) outpatient procedures, totaling to 43/2239 (1.9%) of all biopsies. Major bleeding requiring intervention amounted to 1.0% (0.5% of outpatient procedures). The rate of major bleeding was similar between native and transplant kidneys with clinically insignificant hematomas occurring more often after native kidney biopsies. Of 15 major bleeding episodes in planned outpatient procedures, 12 were detected during the four-hour surveillance period, only three required intervention and none was life-threatening. Risk factors for bleeding were aspirin, low eGFR, anemia, cirrhosis and amyloidosis. Routine post-biopsy ultrasound did not change management.

Conclusions

Kidney biopsy is an overall safe procedure and can be performed as an outpatient procedure in most patients with an observation period as short as four hours. The value of routine post-biopsy ultrasound is questionable.

P 26

A rare cause of hypertension with hypokalemia: a case of reninoma

Yaël Zimmermann [1], Gérard Vogel [1]

1. *Hôpital Riviera Chablais, unit of Nephrology, Rennaz, Switzerland*

Background

Reninoma or juxta-glomerular cell tumor is a usually benign renal renin secreting tumor.

Methods

We report a case of an 18 year old woman, without any medical history, investigated in our hospital's emergency department for a bilateral papillary edema. Ambulatory ophthalmological investigations were performed because of a newly occurring blurry vision, associated with diffuse headaches. MRI and lumbar puncture recommended by the ophthalmologist and neurologist excluded intra-cranial hypertension. The patient presented with severe hypertension.

Results

Laboratory values showed hypokalemia, metabolic alkalosis and microalbuminuria. During the hospital stay, she developed AKIN 1 acute renal injury. Ultrasound revealed a tissular cystic lesion of the superior pole of the right kidney. Abdominal MRI confirmed the lesion and raised suspicion for a renal cell carcinoma without calicial or vascular invasion. Plasma renin value was >500 mUI/L with normal values for plasma aldosterone. Renal biopsy diagnosed a juxta-glomerular cell tumor.

Conclusions

After a more aggressive treatment, hypertension remained well controlled with spironolactone only, finally allowing for withdrawal of all antihypertensive medications. Robot-assisted laparoscopic partial nephrectomy was performed. Studies of the operative specimen confirmed the diagnosis of reninoma. Clinical follow-up showed complete resolution of clinical and biological parameters.

P 27

Relationship between renal function and blood pressure dipping status in renal transplant recipients: A longitudinal study

David Jaques [1], Patrick Saudan [1], Chantal Martinez [1], Axel Andres [2], Pierre-Yves Martin [1], Antoinette Pechère [1], Belen Ponte [1]

1. *Division of Nephrology, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland* ***2.*** *DIvision of Visceral Surgery, Geneva University Hospitals, Geneva, Switzerland*

Background

Hypertension (HT) is associated with adverse outcomes in renal transplant (RTX) recipients. Blunting of physiological decrease in nighttime compared to daytime blood pressure (non-dipping status) is frequent in this setting. However, weather non-dipping is independently associated with renal function decline in RTX patients is unknown.

Methods

We retrospectively screened RTX outpatients attending for a routine ambulatory blood pressure monitoring (ABPM) (T1) at a single tertiary hospital. Patients had two successive follow-up visits, one (T2) and two (T3) years later respectively. Routine clinical and laboratory data were collected at each visit. Mixed linear regression models were used with estimated glomerular filtration rate (eGFR) as the dependent variable.

Results

A total of 124 patients were included with a mean follow-up of 2.12 +/- 0.45 years after ABPM. Mean age and eGFR at T1 were 55.9 +/- 15.1 and 55.6 +/- 21.2 ml/min/1.73 m^2 respectively. 61 patients (50%) had sustained HT and 81 (65.3%) were non-dippers. In multivariate analysis, systolic dipping status was positively associated with eGFR (p = 0.003) and compared to non-dippers, dippers had a 12.3 ml/min/1.73 m^2 higher eGFR. HT was negatively associated with eGFR (p = 0.006).

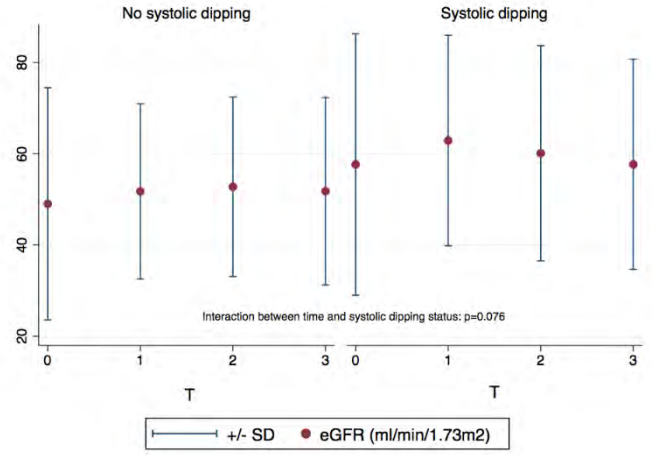
Table 1: Patients characteristics according to systolic dipping status at T1.

Characteristics	Overall (N=124)	Non-dipping (N=81)	Dipping (N=43)	P value
Age (years)	55.9 +/- 15.1	57.8 +/- 14.4	52.5 +/- 15.8	0.06
BMI (kg/m^2)	25.7 +/- 4.0	26.1 +/- 4.2	25.0 +/- 3.6	0.19
Graft vintage (years)	2.70 (0.74 – 6.00)	2.02 (0.69 – 5.00)	2.98 (0.98 – 8.78)	0.06
eGFR (ml/min/1.73m^2)	55.6 +/- 21.2	51.7 +/- 19.1	62.8 +/- 23.0	**0.005**
Proteinuria (g/day)	0.18 (0.12 – 0.31)	0.17 (0.12 – 0.26)	0.27 (0.10 – 0.49)	0.46
Gender (female)	46 (37.1%)	30 (37.0%)	16 (37.2%)	0.98
Smoking	21 (16.9%)	12 (14.8%)	9 (20.9%)	0.38
Diabetes	28 (22.7%)	21 (26.2%)	7 (16.2%)	0.20
Hypertension	105 (85.3%)	70 (87.5%)	35 (81.4%)	0.36
Deceased donor	66 (53.6%)	44 (54.3%)	22 (52.3%)	0.83
Past rejection	22 (17.7%)	13 (16.0%)	9 (20.9%)	0.49
CNI	115 (99.1%)	77 (100%)	38 (97.4%)	0.15
Steroid	77 (66.3%)	54 (70.1%)	23 (58.9%)	0.23
RAA blocker	45 (36.5%)	26 (32.1%)	19 (45.2%)	0.15

Table 2: Factors associated with eGFR over time in multivariable mixed linear regression.

Independent variables	Final model		
	β	95% CI	p
Systolic dipping status	12.39	4.07; 20.70	**0.003**
Time (years)	0.40	-1.19; 2.00	0.61
Dipping*time[a]	-1.74	-4.34; 0.86	0.19
Gender (woman)	2.87	-5.47; 11.21	0.50
Age (years)	-0.23	-0.51; 0.04	0.10
BMI (kg/m^2)	-0.15	-0.96; 0.65	0.71
HT	-12.26	-21.01; -3.52	**0.006**
Diabetes	0.63	-5.46; 6.72	0.83
Graft vintage (days)	-0.73	-2.01; 0.54	0.25
Proteinuria (g/day)[c]	0.51	-1.46; 2.49	0.60
Deceased donor	-3.18	-11.02; 4.66	0.42
Past rejection	-2.67	-10.20; 4.84	0.48
Smoking	3.79	-7.01; 14.60	0.49
CNI	-4.18	-22.36; 13.99	0.65
Steroid	-3.20	-7.44; 1.03	0.13
RAA blocker	-0.58	-4.10; 2.93	0.74

a: Interaction term between systolic dipping status and time



Conclusions

We confirm a high prevalence of non-dippers in RTX recipients. We show that preserved dipping is associated with improved renal function independently of potential confounders, including HT and proteinuria. Whether modification of dipping status by chronotherapy would preserve renal function remains to be tested.

P 28

Significance of bleeding time and other risk factors in transplant and native kidney biopsies*

Céline Fontana [1], Stefan Schaub [2], Matthias Diebold [2], Michael Dickenmann [2]

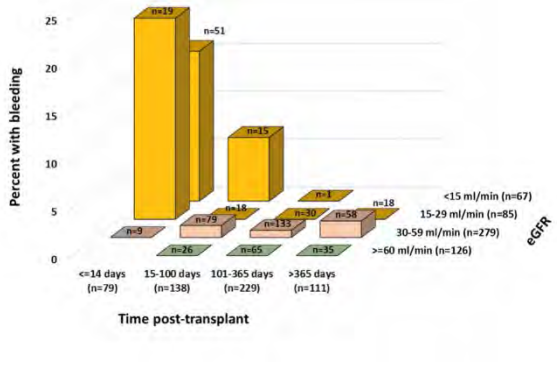
1. *Transplant Immunology and Nephrology, University Hospital Basel, Basel, Switzerland* ***2.*** *Clinic for Nephrology and Transplantation Immunology University Hospital Basel, Basel, Switzerland*

Background

Renal biopsies provide important and decisive information for diagnosis and therapy. We analysed the complication rate after kidney biopsies in native and transplant kidneys and their association with PFA bleeding time, eGFR and various other parameters.

Methods

All patients who had an ultrasound guided kidney biopsy at the University Hospital Basel from 2009 to August 2019 were included. A complication was defined as: need for hospitalisation, ICU stay, significant bleeding (i.e. hemoglobin decrease >10 g/l within 48 hours). Pre-biopsy assessment included: bleeding time, INR, thrombocyte count, eGFR. Univariate and multivariate analysis was performed.



Results

A total of 863 biopsies, 306 native kidney biopsies and 557 transplant kidney biopsies were analysed. Complications were found in 42 biopsies (4.8%), 24 (7.8%) in native kidneys and 18 (3.2%) in transplant kidneys. The following parameters were found to be significant predictors of complications in native kidney biopsies: Type of stay (hospitalized vs outpatient patients, p = 0.003) and prolonged PFA bleeding time (p = 0.03). The following parameters are significantly predictive for the transplant group: time after transplantation (<14 days after transplantation, p <0.0001), platelet count <50x109/l (p <0.0001), prolonged PFA bleeding time (p <0.0001), decreased eGFR <60 ml/min (p <0.0001), and type of biopsy (diagnostic vs surveillance biopsies, p <0.0001). Multivariate analysis revealed abnormal PFA bleeding time and biopsy within 2 weeks post transplant as most significant risk factors. PFA bleeding time correlates significantly with kidney function (p <0.0001). 42% of patients with a eGFR <30 ml/min had a prolonged bleeding time.

Conclusions

In summary, a prolonged PFA bleeding time is the most meaningful parameter for complications after renal biopsy. Transplant biopsies within 2 weeks post transplant provide an additional risk. The PFA bleeding time should be measured in each patient with an eGFR below 30 ml/min and preferably be corrected before biopsy.

**Student paper*

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Lipoprotein glomerulopathy complicated by thrombotic microangiopathy in a patient with an aHUS risk allele of complement factor-H related 1 (CFHR1)

Lara Kollbrunner [1], Patricia Hirt-Minkowski [2], Javier Sanz [3], Elena Bresin [4], Thomas Neuhaus [5], Helmut Hopfer [6], Andreas Jehle [7]

1. *Department of Internal Medicine, Hirslanden Klinik St. Anna, Lucerne, Switzerland ,* ***2.*** *Transplant Immunology and Nephrology, University Hospital Basel, Switzerland ,* ***3.*** *Division of Human Genetics, Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland ,* ***4.*** *Mario Negri Institute for Pharmacological Research, Clinical Research Center for Rare Diseases*

*'Aldo e Cele Daccò', Ranica, Italy , **5.** Children's Hospital of Lucerne, Lucerne, Switzerland , **6.** Institute for Pathology, University Hospital Basel, Basel, Switzerland , **7.** Department of Internal Medicine, Hirslanden Klinik St. Anna, Lucerne & Transplant Immunology and Nephrology, University Hospital Basel, Switzerland*

Background

Lipoprotein glomerulopathy (LPG) is a rare inherited renal disease caused by mutations in the APOE gene, encoding apolipoprotein E. LPG is characterized by glomerular capillary lipid thrombi without significant infiltration by foamy macrophages. Clinically the renal disease manifests with proteinuria with or without an abnormal lipid profile. – Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) characterized by over-activation of the alternative complement pathway. Complement factor H (CFH) is a central inhibitor of the alternative pathway. The complement factor H–related (CFHR) protein family is a group of plasma proteins genetically and structurally related to CFH. CFHR1 polymorphism, resulting from a gene conversion event between CFH and CFHR1, is strongly associated with aHUS. We present a patient with LPG that developed aHUS.

Methods

We used the Sanger Sequencing method to sequence exon 4 of APOE gene. Next-Generation Sequencing was used to analyze genes encoding proteins of the complement system.

Results

A 21-year-old man developed a combined nephritic-nephrotic syndrome in 2012. The kidney biopsy showed LPG (Figure 1). At the end of June 2019 he was referred to our nephrology clinic with end-stage renal disease. His general condition was good. Blood pressure was elevated (170/100 mmHg) and together with the laboratory results (table 1) the diagnosis of TMA was made. We stared dialysis within a few days after admission. Although blood pressure was controlled, the patient showed recurrent thrombocytopenia. Detailed analysis of the complement system revealed a functional complement-defect and the presence of a homozygous aHUS risk allotype CFHR1*B. In addition, sequencing analysis found a pathogenic inframe deletion of APOE gene.

Conclusions

To the best of our knowledge this is the first report of aHUS in a patient with LPG with a documented dysfunction of the complement system and an associated genetic risk factor.

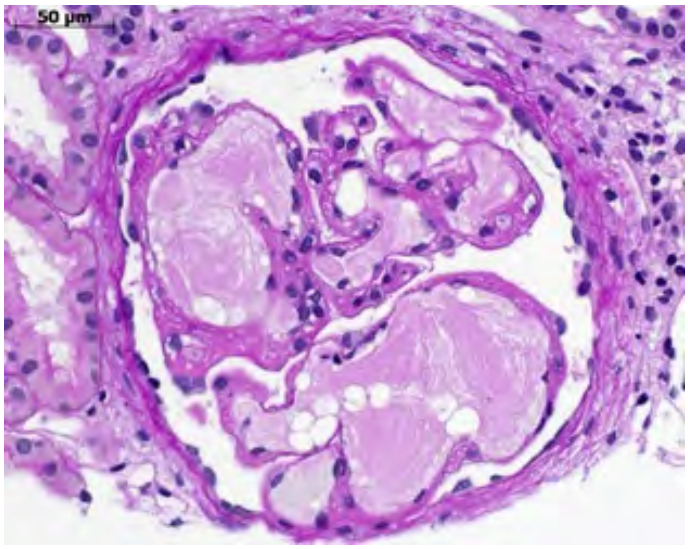

Table 1. Laboratory findings

	at first admission	8-days after	12-days after
a) Blood			
Hematology			
Hemoglobin *(140-180 g/L)*	84 g/L	77 g/L	63 g/L
Fragmentocytes	neg.	neg.	pos.
Platelet Counts *(150-350x10^9/L)*	114x10^9/L	43x10^9/L	51x10^9/L
Chemistry			
Potassium *(3.5-5.1 mmol/L)*	5.49 mmol/L	4.92 mmol/L	4.83 mmol/L
Phosphate *(0.87-1.45 mmol/L)*	2.24 mmol/L	1.97 mmol/L	2.41 mmol/L
Creatinine *(62-106 µmol/L)*	907 µmol/L	1006 µmol/L	985 µmol/L
Urea *(<8.3 mmol/L)*	31.7 mmol/L	29.6 mmol/L	32.3 mmol/L
LDH *(135-225 U/L)*	151 U/L	241 U/L	227 U/L
Haptoglobin *(0.3-2.0 g/L)*	0.47 g/L	<0.1 g/L	NA
Total Bilirubin *(<21.0 µmol/L)*	5.0 µmol/L	7.1 µmol/L	NA
Complement			
C3 *(0.9-1.8 g/L)*	0.81 g/L	0.74 g/L	NA
b) Urine			
Prot/Creat ratio *(<11.3 mg/mmol)*	230 mg/mmol	NA	NA

*NA = non-available

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Cortical perfusion as assessed with contrast-enhanced ultrasound is lower in patients with chronic kidney disease than in healthy subjects and varies according to salt intake

Jonas Garessus 1, Wendy Brito 1, Marielle Hendriks-Balk 1, Grégoire Wuerzner 1, Antoine Schneider 2, Michel Burnier 1, Menno Pruijm 1

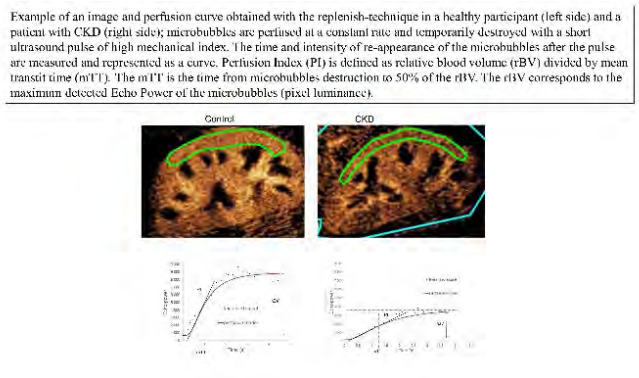
***1.** Nephrology and Hypertension Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, **2.** Adult Intensive Care Unit, University Hospital of Lausanne and University of Lausanne, Lausanne, Switzerland*

Background

Disturbances in renal microcirculation may play an important role in the pathophysiology of chronic kidney disease (CKD), and are possibly influenced by dietary salt intake. However, the lack of reliable and easy accessible techniques hampers thus far an in-depth understanding of the regulation of the microcirculation in humans. The aim of this study was to assess whether contrast-enhanced ultrasonography (CEUS) can identify changes in cortical perfusion induced by different dietary salt intakes in CKD patients and age-matched healthy controls.

Methods

Participants underwent CEUS twice: once after 5 days of high salt intake (HS, >200 mmol/day in healthy controls and >100 mmol/l in CKD), and again after 5 days of low salt diet (LS, <50 mmol/day). Sonovue® (0.015 ml/kg/min) was perfused as contrast agent until a steady state was obtained, followed by four destruction-reperfusion sequences. Outcome measure was the mean perfusion index (PI) of the renal cortex.



Results

Forty healthy volunteers (aged 50±8 years, eGFR 96±13 ml/min/1.73 m²) and 18 CKD stage 2-4 patients (aged 55±11 years, eGFR 54±28 ml/min/1.73m²) were included and underwent CEUS without side effects (see Figure). Under HS conditions, renal PI was significantly lower in CKD patients (1618±1352 vs 3176 ±2278 arbitrary units in controls, p = 0.034). Under LS conditions, renal PI increased in CKD patients (to 2716 ±1540, p = 0.048), whereas PI remained stable in controls (PI 3278±1907, p = 0.86 vs HS). In continuous analysis, PI correlated with eGFR (spearman's r = 0.54, p = 0.005) but not with age, blood pressure or sex.

Conclusions

Contrast-enhanced ultrasound identified important reductions in cortical micro-perfusion in patients with moderate CKD. Lowering salt intake increased cortical perfusion in CKD patients, but not in controls, underlining the possible benefits of a low salt diet in CKD patients. Whether a low perfusion index predicts renal function decline needs further study.

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Tubular water retention is increased during orthostatic stress in obese participants compared to healthy individuals

Nima Vakilzadeh 1, Marc Maillard 1, Eric Grouzmann 2, Grégoire Wuerzner 1

1. Service of Nephrology and Hypertension, Lausanne University Hospital (CHUV), Lausanne, Switzerland 2. Service of clinical pharmacology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Background

Several mechanisms including increased sympathetic nervous system and renin-angiotensin system activity and thus increased tubular sodium reabsorption could explain the increased risk of hypertension in obese population. Lower body negative pressure (LBNP) has been shown to induce a progressive activation of neurohormonal systems, renal tubular and hemodynamic response during the induced orthostatic stress. The objective of this study was to compare the systemic, renal and hormonal responses to lower body negative pressure (LBNP) in healthy (H) and obese (OB) adult participants.

Methods

In this case-control observational study, normotensive OB and H participants were exposed to the LBNP at -20 mbar for 1 hour. Neurohormonal profiles, systemic and renal hemodynamics, as well as renal sodium handling were measured before, during, and after LBNP. Baseline variable and change induced by LBNP were compared using a t-test or a ranksum test as appropriate.

Results

25 H and 29 OB were included in the study. Obese participants were older (33.5 ± 12.1 in vs 42.2 ± 11.3 y in OB) and had higher BMI (22.0 ± 2.1 in H, 36.2 ± 5.4kg/ m^2 in OB). Baseline systolic and diastolic blood pressure, heart rate inulin clearance and renal plasma flow were also higher in obese participants (table 1). During LBNP, the increase in heart rate and urine osmolality and the decrease in free water clearance were higher in obese participants.

Conclusions

Obese participants have an increased renal response to stress characterised by a more pronounced decrease in free water clearance. Renal water handling in obese patients, as a possible pro-hypertensive mechanism, should be investigated in the future.

Table 1 - Hemodynamic, renal and hormonal modifications before and during LBNP

	Healthy individuals (n=25)		Obese individuals (n=29)	
	Baseline	Change induced by LBNP	Baseline	Change induced by LBNP
SBP, mmHg	110.3±9.4	2.7±4.7	132.6 ± 17.8 *	6.2±8.7
DBP, mmHg	64.1±7.8	4.6±3.8	77.1±10.8 *	5.6±8.6
Heart rate, bpm	62.6±7.9	-1.3±4.9	66.6±8.5 *	2.1±5.2¶
Urinary flow rate, mL/min	4.0±1.3	-1.4±4.7	4.6±1.9	-2.2±2.1
Free water clearance, ml/min	0.8±1.1	-0.7±1.3	1.2±1.6	-1.7±1.6¶
Urine osmolality, mOsm/kg	260±122	54.4±140.5	245.2±99.3	148.8±130¶
GFR, ml/min	101.5±25.3	-14.0±26.7	121.6±42.0 *	-8.7±44.2
RPF, ml/min	538±172	-85.6±130.4	811±559 *	-159.0±332.8
FE Na, %	1.7±0.5	-0.05±0.67	1.5±0.85	-0.23±0.47
PRA, ng/ml/h	0.4 (0.3 ; 0.5)	0.1 (0.0 ; 0.2)	0.3 (0.08 ; 0.5)	0.06 (0.0; 0.22)
Aldosterone, pg/ml	28.0 (18.0 ; 43.3)	0.0 (-6.5; 7.1)	41.5 (24.7 ; 57.2)	0.0 (-10.5 ; 12.5)
Norepinephrine, nmol/l	1.1 (0.9 ; 1.4)	0.24 (0.1 ; 0.55)	1.2 (0.8 ; 1.4)	0.36 (0.1 ; 0.53)
Epinephrine, nmol/l	0.09 (0.08 ; 0.12)	0.02 (0.0 ; 0.07)	0.07 (0.05 ; 0.13)	0.03 (0.01 ; 0.08)

Data are expressed as mean ± standard deviation or median (standard deviation). SBP: systolic blood pressure, DBP: diastolic blood pressure, bpm: beats per minute, GFR: measured glomerular filtration rate, RPF measured renal plasma flow, FE Na: fractional excretion of sodium, PRA: plasma renin activity, ARR: aldosterone renin (PRA) ratio.

* p<0.05 Baseline H vs OB (Student t-test or Wilcoxon ranksum test as appropriate)

¶ p <0.05 Δvar H vs Δvar OB (Student t-test or Wilcoxon ranksum test as appropriate)

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Spectrum of renal involvement in patients with myelodysplastic syndromes

Nora Schwotzer 1, Francois Provôt 2, Simon Ville 3, Sebastien Kissling 1, Noemi Jourde-Chiche 4, Alexandre Karras 5, Anne Moreau 6, Jean-Francois Augusto 7, Laurent Daniel 8, Viviane Gnemmi 9, Christophe Bouaka 10, Stanislas Bataille 11, Moglie Le Quintrec 12, Samuel Rotman 13, Fadi Fakhouri 1

1. Nephrology and Hypertension Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland 2. Department of nephrology and renal transplantation, CHRU de Lille, Lille, France 3. Department of nephrology and immunology, CHU de Nantes, Nantes, France 4. Centre de néphrologie et transplantation rénale, hôpital de la Conception, Marseille, France 5. Service de néphrologie, hôpital européen Georges-Pompidou, Paris, France 6. Service de pathologie, CHU de Nantes, CHU Hôtel-Dieu, Nantes, France 7. Service de Néphrologie-Dialyse-Transplantation, Université d'Angers, CHU Angers, Angers , 8. Service d'anatomie et cytologie pathologiques, CHU Timone, Marseille, France 9. Pathology Department, Lille University Hospital (CHU), Lille, France 10. Department of nephrology, Hôpital de Martigues, Martigues, France 11. Institut Phocéen de néphrologie, Clinique Bouchard, Marseille, France 12. Département de Néphrologie, CHU Montpellier, France 13. CHUV, Institut de Pathologie, Lausanne, Switzerland

Pt	Gender Age (y)	MDS type	Treatment at KB	Time between MDS and KB (y)	At time of KB				Extra-renal manifestations	Diagnosis/KB	TRT	Outcome
					SCr (mg/dL)	U P/Cr (g/g)	H	CRP (mg/L)				
1	M, 74	MLD	EPO	3	6.2	Anuria	+++	229	Fever, livedo, scleritis, polychondritis, coeliac disease.	Acute TIN	Cs	CKD: SCr 1.6-1.8 mg/dL (eGFR 36 ml/min/1.73 m2) at 1 year.
2	M, 76	RS	EPO	2	3.2	0.3 g/L	-	29	-	Acute TIN	Cs	SCr 9.5 mg/dL (eGFR 74 ml/min/1.73m2) and U P/Cr < 0.5 g/g at 5 months.
3	M, 74	Isolated (5q) deletion	EPO	> 1 y	2.9*	4.7	+	17	Polychondritis.	Acute TIN (TMA)	-	ESRD at 1 month.
4	F, 76	RAEB2	Azacitidin	1.5	4.5	0.6	+++	115	Fever, arthralgia, buccal ulcerations, skin nodules.	Acute TIN		CKD: SCr 2.5 mg/dL (eGFR 18 ml/min/1.73m2) at 3 years.
5	M, 83	NA	-	Concomitant	1.9	0.8 g/L	-	13	Arthralgia.	Acute TIN	Cs	CKD: SCr 1.4 mg/dL (eGFR 46 ml/min/1.73m2) at 3 months.
6	F, 60	MDS-MPS	-	Concomitant	16/ HD	0.7	-	NA	Pericarditis.	Acute TIN	Cs	HD and death (septic shock) two months later.
7	M, 80	MLD	EPO, Azacitidin	1.6	3.6	1.5	++	50	-	Acute TIN IgAN		ESRD (patient declined dialysis) and Death 1 year later (AML).
8	M, 79	NA	EPO, deferoxamin	7	8.3*	0.6	+++	142	-	Subacute TIN	None	ESRD at 1 month.
9	F, 69	EB	RBC transfusions	1.5	3.7	3.9**	+++	50	Neutrophilic urticaria, sicca syndrome.	ANCA-negative PIGN	Cs+MMF+AZA	ESRD at 6 months.
10	M, 74	MLD	RBC transfusions, EPO, deferoxamin	MDS diagnosed 2 weeks after KB	4	1.1	+++	319	Fever, pleuritis.	ANCA-negative PING	Cs+CYP[a] RTX	CKD: SCr 2.4 mg/dL (eGFR 25 ml/min/1.73m2) at 6 years.
11	M, 73	EB	EPO, GM-CSF	8	5.1/HD	2.3g/L	+++M	76	Thrombocytopenia	ANCA-negative PING	Cs+RTX	SCr decreased to 2 mg/dL at 3 weeks but increased again following septic shock and HD was restarted.
12	M, 74	RS-SLD	-	2 months after KB	2.5	9.4***	+	1	Sicca syndrome, peripheral neuropathy.	MN	Cs+MMF RBC Transfusions	Partial remission of the NS at 8 months (Alb, 38 g/L, Puria 1.4 g/24h). Stable CKD: SCr 1.25 mg/dL (eGFR 51 ml/min/1.73m2).
13	F, 72	MLD	EPO, RBC transfusions.	1	1.3	7.9[g]	-	5	-	MN	ACEI	Stable CKD: SCr 1.5 mg/dL (eGFR 35 ml/min/1.73m2) and Puria 2 g/day at 15 months.
14	F, 78	SLD	EPO	> 3	1	0.8	+++	35	Purpura, skin leukocytoclasic vasculitis.	HSP	-	Stable CKD: SCr 0.9 mg/dL (eGFR 58 ml/min/1.73m²) and proteinuria (< 1g/24h) at 8 years
15	M, 69	MLD	-	Concomitant	1.4	1	+++		-	IgAN	None	Stable CKD: SCr 1.4 mg/dL (eGFR 50 ml/min/1.73m2) at 2 years.
16	M, 63	MDS-MPS	Azacitidin	1	1.6	0.2	++	< 5	-	Ig-MPGN type 1	None	Stable CKD: SCr 2 mg/dL (eGFR 33 ml/min/1.73 m2). Death 6 years later (AML).
17	M, 67	EB	-	Concomitant	2.6	0.5	+	112	Arthralgia, livedo.	Crescentic C3G[b] Acute TIN.	Azacitidin, EPO Cs+RTX Ecu	ESRD at 3 months.
18	F, 75	MLD	EPO	1 month	4.5	11	+++	32	-	Crescentic IgG GN	Cs, RTX	CKD: SCr 2.7 mg/dL (eGFR 24 ml/min/1.73m2) at 3 months.
19	M, 80	RS	RBC transfusion	2	0.6	9.7 g/l*	-	Nal	-	MCD	Cs	Partial remission of NS. Death 1 month later (septic shock).
20	M, 80	Unclassifiable	RBC transfusions, EPO, GM-CSF, deferoxamin	4	0.6	1.24	+++	123	Peripheral neuropathy.	Normal	Cs	Stable normal SCr. Normalization of Puria (0.3 g/24h).

Background

Myelodysplastic syndromes (MDS) are a heterogeneous group of primary clonal disorders defined by ineffective haematopoiesis with dysplasia in one or several hematopoietic cell lineages leading to cytopenias. MDS are also characterized by a unique high prevalence of associated autoimmune manifestations reported in 10-20% of patients. Kidney is a major target of autoimmunity. Renal involvement has only been rarely reported in patients with MDS. We aimed to describe the spectrum of pathological features in kidney biopsies in patients with MDS.

Methods

We retrospectively identified adult (>18 years of age) patients with MDS who had undergone a kidney biopsy in nine university and general hospital centers in France and Switzerland.

Results

Twenty patients with MDS who had undergone a kidney biopsy between 2001 and 2019 were included. Detailed pathology findings in kidney biopsies are shown in table 1. The most frequent feature in kidney biopsies was acute tubulointerstitial nephritis (TIN) present in eight (40%) patients. Other pathological features included: ANCA-negative pauci-immune necrotizing glomerulonephritis (n = 3), membranous nephropathy (n = 2), IgA nephropathy (n = 1), immunoglobulin-associated membranoproliferative glomerulonephritis type I (n = 1), crescentic C3 glomerulopathy (n = 1), crescentic IgG glomerulonephritis (n = 1) and minimal change disease (n = 1).

Conclusions

The present study is the first description of the spectrum of renal diseases documented by kidney biopsy in patients with MDS. It clearly indicates that the kidney, along with other organs, is a target of autoimmunity in the setting of MDS. The predominant pathological feature in our series was acute TIN present in 40% of cases. The other renal pathological findings in MDS patients from this series encompass a wide range of autoimmune glomerulonephritis. In total, MDS is associated to several autoimmune renal manifestations, predominantly acute TIN, and more rarely several complex glomerulonephritis.

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Association of urinary sex steroid hormones with urinary calcium, oxalate and citrate excretion in kidney stone formers

Daniel Fuster [1], Gaétan Morard [1], Lisa Schneider [1], Cedric Mattmann [1], David Lüthi [1], Bruno Vogt [1], Nasser A. Dhayat [1]

1. Inselspital, Bern University Hospital, University of Bern, Department of Nephrology and Hypertension, Bern, Switzerland

Background

Sex-specific differences in nephrolithiasis with respect to both distribution of prevalence and stone composition are widely described and may be influenced by sex hormones.

Methods

We conducted a cross-sectional analysis of the relationship between 24-hour urinary sex hormone metabolites measured by gas chromatography–mass spectrometry with urinary calcium, oxalate and citrate excretion in a cohort of 628 kidney stone formers from a tertiary care hospital in Switzerland, taking demographic characteristics, kidney function and dietary factors into account.

Results

We observed a positive association of urinary calcium with urinary testosterone and 17β-estradiol. Positive associations of urinary calcium with dehydroepiandrosterone, 5α-DH-testosterone, etiocholanolone, androsterone, and estriol were modified by net gastrointestinal alkali absorption or urinary sulfate excretion. As the only sex hormone, dehydroepiandrosterone was inversely associated with urinary oxalate excretion in adjusted analyses. Urinary citrate correlated positively with urinary testosterone. Associations of urinary citrate with urinary androsterone, 17β-estradiol and estriol were modified by urinary sulfate or sodium, or by sex.

Conclusions

Urinary androgens and estrogens are significantly associated with urinary calcium and citrate excretion, and associations are in part modified by diet. Our data furthermore reveal dehydroepiandrosterone as a novel factor associated with urinary oxalate excretion in humans.

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Young Woman with Recurrent Fractures - A Case Report

Lukas Gerber [1], Florian Buchkremer [1], Sylvia Hoeller [2], Daniel Baumhoer [2], Alexander Cornelius [3], Andreas H. Krieg [4]

1. Department of Nephrology, Dialysis and Transplantation, Kantonsspital Aarau, Switzerland , 2. Bone Tumor Reference Center at the Institute of Medical Genetics and Pathology, University Hospital Basel and University of Basel, Switzerland , 3. Department of Radiology, Kantonsspital, Aarau, Switzerland , 4. Bone and Soft Tissue Tumor Center of the University of Basel (KWUB), Basel, Switzerland

Background

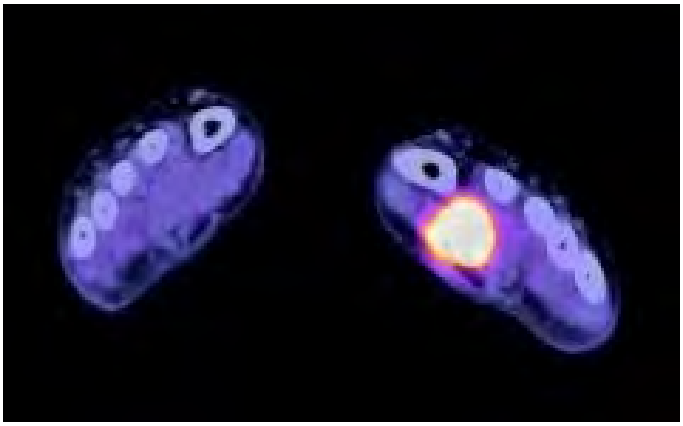
A previously healthy 22-year-old woman presented with lumbar back pain for 6 months in 2010. MRI and bone scintigraphy suggested a spondylarthropathy. She received treatments with steroids and various immunomodulatory drugs (Etanercept, Adalimumab) with limited success. After a pelvic fracture, osteoporosis was diagnosed (osteodensitometry showing a T-Score of -3.0). Despite treatment with denosumab followed by teriparatide she continued to have fractures with minimal traumas requiring crutches to walk.

Methods

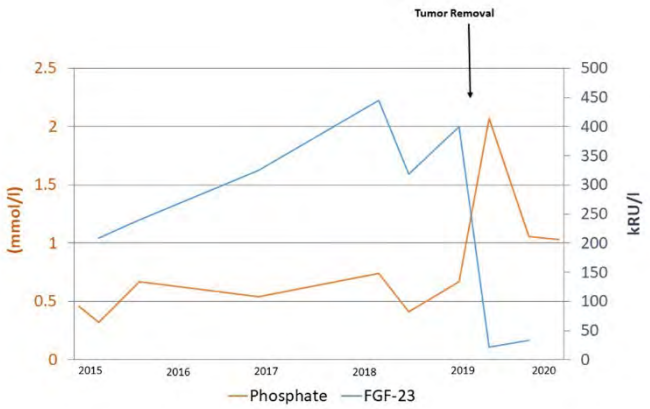
In 2015 she was found to have hypophosphatemia at 0.42 mmol/l secondary to renal phosphate wasting (fractional excretion of phosphate 16%; TmP/GFR 0.22 mmol/l). Serum calcium and PTH levels were normal, alkaline phosphatase was high. A diagnosis of osteomalacia was made. Serum FGF-23 was markedly elevated at 209 kRU/l (normal range 26-110). Possible underlying causes included a tumor, hereditary conditions and intravenous iron administrations. An FDG-PET scan, however, did not reveal a tumor and next-generation sequencing as well as multiplex ligationdependent probe amplification of all known causative genes were negative. She had never received intravenous iron. Meanwhile, her symptoms improved significantly on oral phosphate and calcitriol as well as regular physiotherapy. A repeat osteodensitometry showed a normalization of the T-score.

Results

In 2018 we performed a DOTATOC -PET/CT-scan, which showed a (clinically non-apparent) tumor (Fig 1) in her left forefoot which had not been visible in the previous FDG-PET.



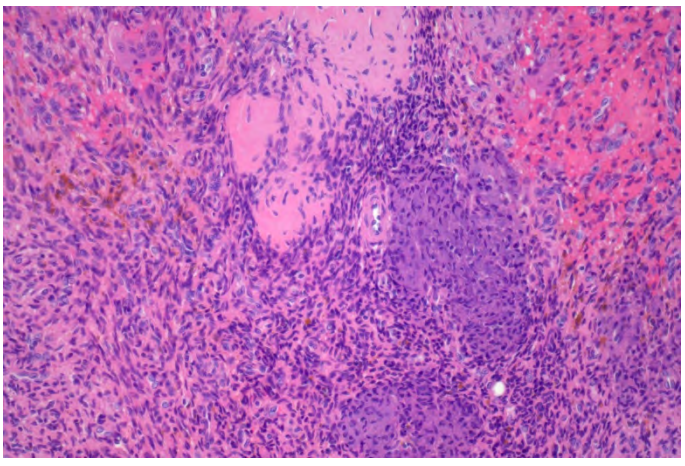
After complete removal, FGF-23 levels normalized and the renal phosphate leak disappeared (Fig 2).



The histology showed typical findings of a phosphaturic mesenchymal tumor (PMT) (Fig 3).

Conclusions

Tumor-induced osteomalacia is a rare but increasingly recognized condition, caused by mostly benign and slowgrowing PMT secreting FGF-23. In 60% of the cases (including ours) a translocation FN1-FGFR1 is detectable. Our case illustrates the common difficulties in diagnosing and treating these tumors with a time lag of 9 years between the onset of symptoms and tumor resection.



P 35

The unwelcome connection from lung cancer to glomeruli: a case report

Manuela Nickler 1, Ingeborg Fischer 2, Luca Bernasconi 3, Elion Hoxha 4, Thorsten Wiech 5, Sarosh Irani 6, Peter Moosmann 7, Min Jeong Kim 1

1. Clinic for Nephrology, Kantonsspital Aarau, Aarau, Switzerland 2. Institute for Pathology, Kantonsspital Aarau, Aarau, Switzerland 3. Zentrum für Labormedizin, Kantonsspital Aarau, Aarau, Switzerland 4. III. Medizinische Klinik und Poliklinik - Nephrologie, Universitätsklinikum Hamburg-Eppendorf, Germany, 5. Institut für Pathologie, Universitätsklinikum Hamburg-Eppendorf, Germany 6. Klinik für Pneumologie, Kantonsspital Aarau, Aarau, Switzerland 7. Klinik für Onkologie, Kantonsspital Aarau, Aarau, Switzerland

Background

Despite an association between membranous nephropathy (MN) and malignant tumours has been known for decades, the underlying mechanism remained mostly unclear. Recently the pathogenic role of Thrombospondin-type-1-domain-containing7A (THSD7A) antigen for MN has been reported in association with mostly gastrointestinal or genitourinary tumours.

Results

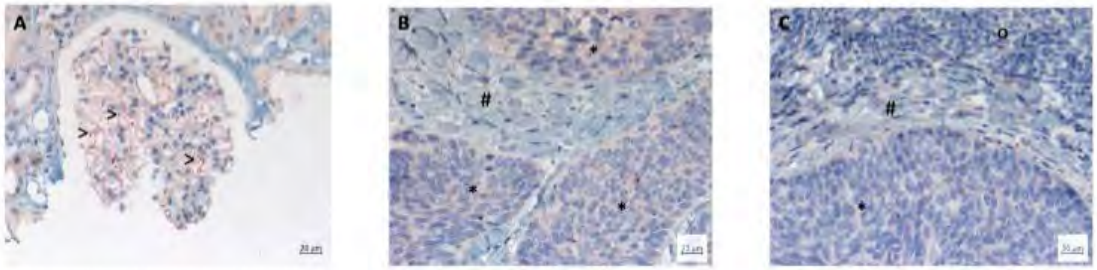
We report a case of a 58-year-old male with severe nephrotic syndrome caused by MN with concomitantly diagnosed squamous-cell cancer (SCC) of left lung with mediastinal infiltration and lymph nodes metastases. At initial presentation, urinary protein excretion was about 23g per day and serum albumin was not measurable, because the concentration was too low. The kidney function was impaired with eGFR 30 ml/min/1.73 m^2 (CKDEPI). Anti-phospholipase-A2-receptor-1 antibody was not detected. Since an association between the cancer and MN was highly likely, neoadjuvant chemotherapy with carboplatin and paclitaxel and ultimately the resection of left upper lobe and mediastinal pleura and lymph node dissection were conducted in the following 5 months, and no immunosuppressive therapy was commenced. There was however no improvement of nephrotic syndrome during and after the cancer therapy. Upon further diagnostic work-up, anti-THSD7A antibody was detected in the serum of initial presentation at a titre of 1:1000. We were able to detect THSD7A antigen in the tissues of lung cancer, lymph node and glomeruli by immunohistochemistry (Figure).

Six months after the operation, there is no evidence for cancer recurrence, MN is however highly active with urinary protein excretion of about 20 g per day, slowly deteriorating kidney function and persistent positive anti-THSD7A antibody (last titre 1:100). We therefore commenced B-cell depleting therapy with Rituximab and the response is awaited in the following months.

Conclusions

This is the first case demonstrating the pathogenic role of THSD7A for MN in association with lung SCC. Due to persistent nephrotic syndrome along with positive anti-THSD7A-antibody, B-cell depleting therapy has been recently commenced.

Figure: THSD7A staining in glomerulus (A), primary lung tumor (B) and lymph node (C)



Enhanced granular staining for THSD7A (red) at the outer aspects of the glomerular basement membranes at the location of the subepithelial immune deposits (>)

Weak cytoplasmic positivity for THSD7A in the tumor cells (*) but not in the stroma cells (#)

Weak cytoplasmic positivity for THSD7A in the tumor cells (*) but neither in the stroma cells (#) nor in the lymphocytes (o)

P 36

A standardized and simplified triple therapy combined with electronic monitoring of adherence normalizes 24 h ambulatory blood pressure (BP) in at least one third of patients with apparent resistant hypertension

Erietta Polychronopoulou 1, Maxime Berney 1, Renate Schoenberger 2, Georg Ehret 3, Antoinette Pechère 4, Michel Burnier 1, Grégoire Wuerzner 1

1. Nephrology and Hypertension Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland 2. Service of cardiology, Luzerner Kantonsspital, Lucerne, Switzerland 3. Division of Cardiology, Geneva HUG, Geneva, Switzerland 4. Division of Nephrology, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland

Background

Lack of adherence to antihypertensive drugs is one of the most common factor explaining a poor BP control in patients with apparent resistant hypertension. Few studies have used a standardized treatment coupled to electronic adherence monitoring in patients with apparent resistant hypertension. The objective of this study was to determine the rate of BP control based on 24h ambulatory BP monitoring (ABPM) when prescribing a standardized triple therapy associated with electronic monitoring of drug intake for 3 months.

Methods

Patients with at least three antihypertensive drugs and residual hypertension on 24 hour ABPM were recruited. A single pill combination of olmesartan 40 mg and amlodipine 10 mg was prescribed together with 25 mg chlorthalidone for 3 months. Medications were provided in 2 separated electronic pills boxes (MEMS®) recording the date and time. Patients were seen at 6 and 12 weeks. At 3 months, we performed a second ABPM and analyzed MEMS® data.

Results

Forty-nine patients (36% women) were included: 36 had complete data sets. Overall, mean 24h systolic BP (SBP) decreased from 148±19 mmHg to 129±16 mmHg ($p < 0.001$) and diastolic BP (DBP) decreased from 89.0±16.1 mmHg to 77.5±10.5 mmHg ($p < 0.001$). Fifty percent of patients normalized SBP and 36% normalized both SBP and DBP. Median taking adherence (%) was respectively 92.5% (interquartile range (IQR) 84.0-100) and 91.9% (IQR 83.0-100) for the fixed combination and chlorthalidone. When analyzed according to tertiles of adherence, decreases in SBP were respectively 27±16.6 mmHg in tertile 1(99-100%), 20±31 mmHg in tertile 2 (89-98.9%) and 9.1± 15.4 mmHg. in tertile 3 (0-88%) ($p = 0.027$ for trend).

Conclusions

Simplified standardized antihypertensive therapy together with an electronic monitoring of adherence normalizes BP in more than 1/3 of patients with apparent resistant hypertension. BP reduction correlates with the level of adherence. This diagnostic and supportive strategy may prevent unnecessary investigations or interventions.

P 37

Reference data for anthropometric calculations of body surface area, creatinine excretion rate and total body water - Adults, United States, 2015-2018

Florian Buchkremer [1], Stephan Segerer [1]

1. *Department of Nephrology, Dialysis and Transplantation, Kantonsspital Aarau, Switzerland*

Background

Anthropometric calculations based on weight and height are widely used in medicine. Body mass index is probably the most prominent example. Whereas reference data for its population-wide distribution are available, these are lacking for other commonly used calculations. In this report, we provide population level data for anthropometric equations of renal interest, notably body surface area, creatinine excretion rate and total body water.

Methods

The National Health and Nutrition Examination Surveys (NHANES) conducted by the National Center for Health Statistics provide information on age, gender, race, weight and height of the non-institutionalized civilian population of the United States. We calculated total body water, creatinine excretion rate and body surface area for study participants. Following recommended methodology with sample weights, primary sampling units and strata provided by NHANES we then obtained the mean, standard error of the mean and 5th, 10th, 15th, 25th, 50th, 75th, 85th, 90th and 95th quantile values of the respective anthropometric estimates on a population level. We did this for males and non-pregnant females 20 years of age and over for body surface area, 20-79 years of age for creatinine excretion rate and total body water.

Results

The results are provided in tabular form. All tables depict values for the non-institutionalized civilian United States population for the years 2015 to 2018 across all racial and Hispanic-origin groups. As an example the data for body surface area demonstrate that the usual standard value of 1.73 m^2, does not apply to the current US population at all. The wide range underscores the necessity to correct eGFR for actual BSA when using it for drug dosing.

Conclusions

Our tables should help clinicians appraise values of body surface area, creatinine excretion rate and total body water in individual patients. They allow up-to-date specifications of average values and common ranges for these equations.

P 38

Impact of Covid-19 pandemic lockdown on renal patients care. The experience of a single Swiss center

Claudia Ferrier [1], Paola Rodoni-Cassis [2], Bruno Vogt [3]

1. *NefrocentroTicino and Inselspital University Hospital, Berne, Switzerland* ***2.*** *Clinica St. Anna, Lugano ,* ***3.*** *Inselspital University Hospital, Berne, Switzerland*

Background

Following the Covid-19 pandemic, between March and April 2020 a lockdown was imposed by government to avoid overload and failure of hospitals capacity. During lockdown, regular health care services were interrupted and outpatients clinics were restricted to emergencies only. Elderly people over 65 faced severe confinement rules and many of them remained in voluntary self-isolation for several weeks after the easing of restrictions. The aim of the present survey was to analyze the consequences of lack of regular follow-up on high-risk renal patients due to the Covid-19 pandemic.

Methods

Clinical data, renal disease related-complications and co-morbidities were recorded in high-risk renal patients who were subject to tight controls, but attended the Nefrocentro several weeks after lockdown was lifted. We recorded the decrease in renal function with related complications and delays in diagnosing potentially irreversible conditions.

Results

Among all the patients and staff of the Nefrocentro, none were found to be Covid-19-positive so far. Twenty-two high-risk patients required frequent follow-up. Of those patients, 2/22 (9%) presented with uncontrolled blood pressure (BP) and 1/22 (5%) had kidney stones. Nineteen (19/22) (86%) had impaired renal function (G2-G4) and 8/19 (42%) showed a further decrease, ranging from stage G3-G5 at the end of lockdown. In the remaining 11 patients with impaired renal function without further decrease, we observed two statin-induced rhabdomyolyses. Moreover, we found delays in the diagnosis of concomitant pathologies, one lymphoma in a transplant patient, one parathyroid adenoma and three major infections, including one septic shock, due to obstructive kidney stones.

Conclusions

The interruption of regular follow-up of high-risk renal patients was followed by adverse outcome in kidney function, associated complications and delayed diagnosis of other pathologies. This survey underlines the importance of the patient-physician relationship and suggests that telemedicine alone might not be an alternative solution in lockdown situations.

P 39

Uric Acid Stone Formers in the Swiss Kidney Stone Cohort – NCCR KIDNEY.CH project *

Joachim Zahnd [1], Daniel Fuster [2], Nasser A. Dhayat [2], Harald Seeger [3], Alexander Ritter [3], Thomas Ernandez [4], Catherine Stoermann-Chopard [4], Florian Buchkremer [5], Stephan Segerer [6], Grégoire Wuerzner [7], Sandra Schafroth [8], Tanja Haeusermann [8], Beat Roth [9], Carsten Wagner [10], Olivier Bonny [11]

1. *University of Lausanne, Lausanne, Switzerland ,* ***2.*** *Inselspital, Bern University Hospital, University of Bern, Department of Nephrology and Hypertension, Bern, Switzerland,* ***3.*** *Universitätsspital Zürich, Klinik für Nephrologie, Zürich, Switzerland* ***4.*** *HUG, Néphrologie, Genève, Switzerland ,* ***5.*** *Kantonalspital Aarau, Nephrologie, Dialyse und Transplantation, Aarau, Switzerland* ***6.*** *Department of Nephrology, Dialysis and Transplantation, Kantonsspital Aarau, Switzerland* ***7.*** *Nephrology and Hypertension Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland* ***8.*** *NCCR Kidney.CH, Zurich, Switzerland* ***9.*** *CHUV, Service de Urologie, Lausanne, Switzerland* ***10.*** *Institute of Physiology, University of Zurich, Zurich, Switzerland* ***11.*** *CHUV, Service de Néphrologie, Lausanne, Switzerland*

Background

About 10% of kidney stones contain uric acid (UA). UA stones result from specific physiopathological processes that can be summarized in three main patterns: low urinary pH (acidification), hyperuricosuria with normal fractional excretion of UA (FEUA) (overproduction) and hyperuricosuria with high FEUA (renal leak). This study aims at categorizing stone formers by their UA phenotypes.

Methods

We used data from 768 patients of the Swiss Kidney Stone Cohort (SKSC) who were investigated by two 24h urine collections and blood analysis. We studied patients' phenotypes according to FEUA, urinary pH and uricosuria. Finally, we analyzed the patients' phenotypes based on stone composition (mixed UA-CaOx or pure UA stones).

Results

Patients presenting hyperuricosuria and high FEUA (*i.e.* ≥10%) had lower serum UA (SUA) and accounted for 3.1% of all SKSC patients. More women were found in that category suggesting a role of sexual hormones in the renal UA leak. By contrast, hyperuricosuria with normal FEUA was mostly seen in men, was present in 93% of hyperuricosuric patients and was positively associated with BMI. High BUN level and low urinary pH suggested that hyperuricosuria was the consequence of an animal-protein rich diet. In the same line, hyperuricosuric stone formers had higher calciuria and natriuresis. Regarding stone composition analysis, we found 5.75% mixed UA-CaOx stones and 3.45% pure UA stones. Pure UA stones were associated with lower urinary pH. Hyperuricosuria was present in 41% of CaOx stone formers, 46% of mixed UA-CaOx stone formers and 66% of pure UA stone formers, suggesting a major role in stone formation.

Conclusions

This study identifies UA renal leak as a cause of hyperuricosuria in 3.1% of stone formers. Hyperuricosuria with normal FEUA is most probably the result of dietary habits that might be amenable to targeted intervention.

** Student paper*

P 40

Lyso-Gb3 associates with adverse long-term outcome in patients with Fabry disease

Albina Nowak 1, Felix Beuschlein 1, Visnuka Sivasubramaniam 1, David Kasper 2, David Warnock 3

1. University Hospital of Zurich, Zurich, Switzerland 2. ARCHIMED Life Science GmbH, Vienna, Austria 3. University of Alabama at Birmingham, The United States

Background

Fabry disease (FD) is a rare X-linked lysosomal storage disease caused by mutations in the α-galactosidase A (*GLA*) gene leading to deficiency of α-galactosidase A and ultimately in progressive glycosphingolipid accumulation, especially globotriaosylceramide (Gb3) and its deacylated derivative Lyso-Gb3.

Methods

In a cohort of 66 genetically confirmed FD patients (26 males and 40 females), we analysed serum Lyso-Gb3 as a factor associated with adverse clinical outcomes in a long-term study. The main outcome was a composite endpoint of incident renal replacement therapy, atrial fibrillation, pacemaker and/or ICD implantation, cerebrovascular events or death, whichever occurred first.

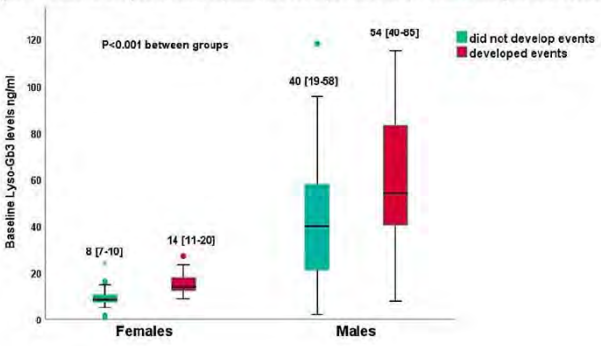
Table 1. Hazard Ratios [1] (and 95% CIs) for occurrence of primary endpoint [2] according to the baseline serum Lyso-Gb3 levels and the pretreatment Lyso-Gb3 exposure, both per natural log increase.

	Baseline Lyso-Gb3 levels			Pretreatment exposure to Lyso-Gb3		
	HR	95%CI	P	HR	95%CI	P
Crude	2.12	1.32-3.42	0.002	3.02	1.69-5.37	<0.001
Model 1	2.45	1.44-4.14	0.001	2.88	1.58-5.25	0.001
Model 2	3.75	1.44-9.73	0.007	3.69	1.60-8.51	0.002
Model 3	4.62	1.55-13.81	0.006	3.41	1.11-10.49	0.03

[1] Model 1: adjusted for age at Lyso-Gb3 determination; Model 2: additionally adjusted for male sex; Model 3: additionally adjusted for Classic phenotype.

[2] Primary endpoint was defined as a composite of first occurrence of renal replacement therapy requirement (kidney transplant or chronic dialysis), new onset of atrial fibrillation, pacemaker and/or ICD implantation, myocardial infarction, cerebrovascular events (stroke or TIA), death.

Figure 1. Baseline serum Lyso-Gb3 levels in patients who developed events versus no events during the observational period.



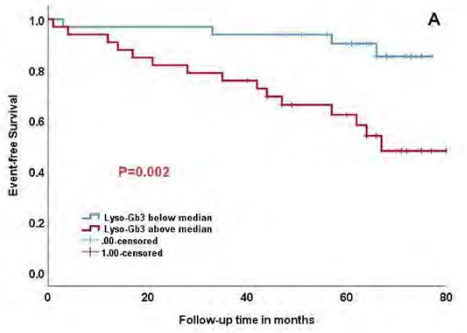
Results

During the median follow-up time of 68 (40-80) months, events occurred in 19 (29%) of the patients. In a Cox regression analysis, Lyso-Gb3 levels (HR 4.62 [1.55-13.81] P = 0.006) and the pretreatment exposure to Lyso-Gb3 (HR 3.41 [1.11-10.49) P = 0.03) (both per SD increase) were significantly associated with adverse outcomes, even after adjustment for other co-variates (Table 1). In males and females, serum levels of Lyso-Gb3 were significantly higher in patients who developed events versus patients without events (Figure 1). In the Kaplan-Meier analysis, the median of plasma Lyso-Gb3 levels (Figure 2) and of the cumulative pretreatment Lyso-Gb3 exposure separated patients with versus without clinical events. If pretreatment Lyso-Gb3 exposure was added to multivariable logistic regression models containing age, sex, phenotype and ERT as other covariates and the composite outcome as dependent variable, the AUC for the composite outcome significantly improved from 0.72 to 0.86 (P comparison = 0.04).

Conclusions

Lyso-Gb3 is a significant, independent risk factor associated with important clinical events. Whether treatment related amelioration of Lyso-Gb3 exposure will improve long-term outcome needs to be established in prospective interventional trials.

Figure 2. Time to first complication in Fabry patients according to serum Lyso-Gb3 levels (A) and the pretreatment exposure to Lyso-Gb3 (B), grouped as above and below median.



P 41

A case-report of combined Shiga-toxin associated hemolytic uremic syndrome and heparin-induced thrombocytopenia

Elia Rigamonti 1, Tecla Bonora 1, Mariangela Ventresca 1, Giulia Bedino 1, Elena Galfetti 2, Pietro Cippà 1

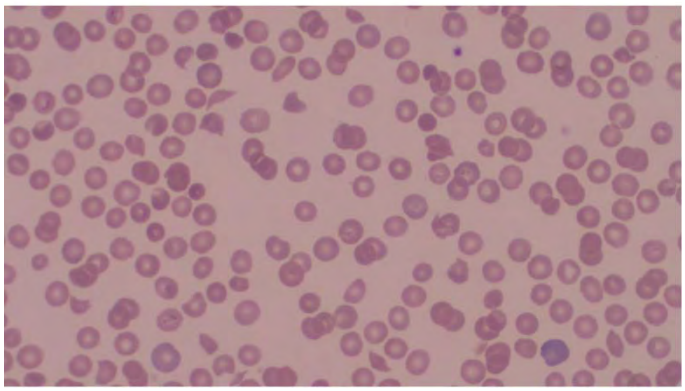
1. Division of Nephrology, Ente Ospedaliero Cantonale, Lugano, Switzerland , 2. Division of Hematology, Istituto Oncologico della Svizzera Italiana, Bellinzona, Switzerland

Background

The combination of acute kidney injury and severe thrombocytopenia requires a systematic diagnostic approach and rapid therapeutic intervention. We report a case of an elderly woman with an unusual presentation of thrombotic microangiopathy (TMA).

Methods

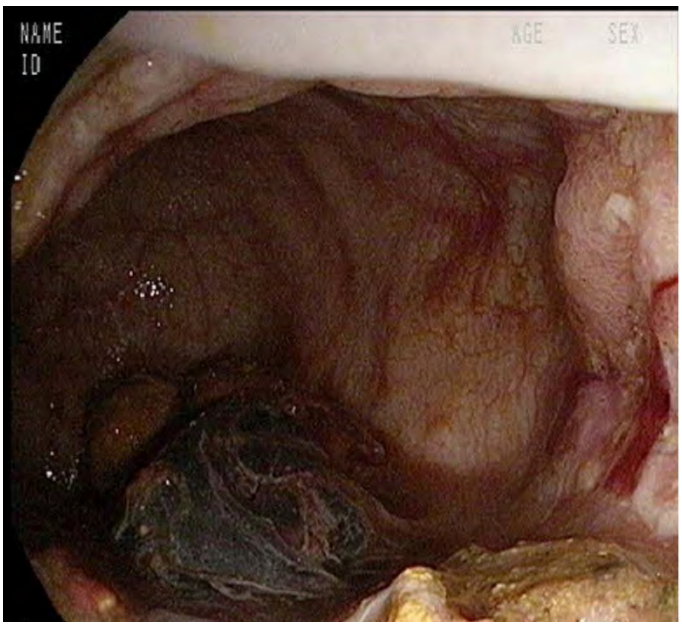
Case. A 79-year-old woman was admitted to the surgical unit because of proctitis, after self-emptying of a fecal occlusion. A few days after admission, a nephrological evaluation was requested because of acute kidney injury (AKI stage 3), severe thrombocytopenia (15x109/l), hemolytic anemia and mild neurological deterioration. In the suspicion of thrombotic thrombocytopenic purpura (TTP) we started therapy with high-dose corticosteroids, and plasmapheresis. Secondary causes of TMA were excluded (drugs, viral infections, autoimmunity, paraneoplastic). C3 and C4 levels were initially normal, anti-factor H antibodies were not present. Fecal cultures, obtained only a week later due to constipation, showed the presence of Shiga toxin producing Escherichia coli, thereby setting the diagnosis of hemolytic uremic syndrome (HUS). Plasmapheresis was therefore stopped.



Results

Under supportive therapy, the clinical conditions, the renal function and the hemolytic anemia slowly improved, but thrombocytopenia persisted over several weeks and the patient developed posterior tibial vein throm-

bosis despite prophylactic doses of heparin. With a strong clinical suspicion of heparin induced thrombocytopenia (HIT), Heparin was immediately discontinued and anticoagulant therapy with argatroban was started. Antibodies to platelet factor 4 were positive, and heparin-induced platelet aggregation (HIPA) assay confirmed the diagnosis of HIT. The evolution was favorable: the patient was discharged in good clinical conditions, with normal platelet count.



Conclusions

To our knowledge, this is the second reported case of combined HUS/HIT (Studt JD, Hemostaseologie 2013). TMA leads to platelet activation with release of PF4 in a highly inflammatory environment, which might trigger HIT. A discordant evolution of the platelet counts in patients with TMA requires a systematic re-evaluation of the thrombocytopenia.

P 42

Antineutrophil cytoplasmic antibody-associated vasculitis and Epstein–Barr virus primoinfection

Salome Gastberger 1, Norbert Arn 2, Birgit Helmchen 3, Andreas Kistler 1

1. *Department of Internal Medicine, Division of Nephrology, Cantonal Hospital Frauenfeld, Frauenfeld, Switzerland* ***2.*** *Institut of Nephrology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland* ***3.*** *Institute of Pathology, University Hospital Zürich, Züric, Switzerland*

Background

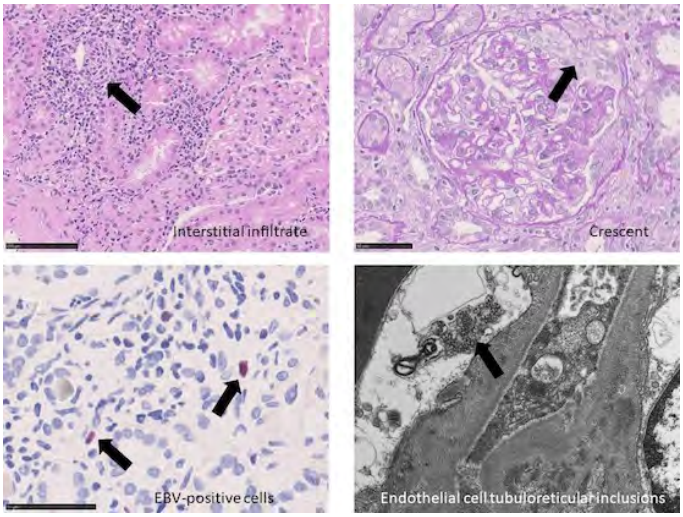
The pathogenesis of antineutrophil cytoplasmic autoantibody (ANCA) - associated vasculitis (AAV) remains unclear. Infections may trigger autoimmunity. Here, we report a case of concomitant Epstein Barr virus (EBV) primoinfection and AAV.

Methods

We performed ANCA testing, serology and PCR for EBV as well as kidney biopsy including Epstein–Barr encoding region (EBER) in situ hybridization.

Results

A 76-year old man with a 3-week history of night sweats and general fatiguewasadmitted to our hospital. On admission, marked lymphocytosis (10.4G/L), reduced kidney function (creatinine 224 µmol/L, eGFR 25ml/min/1.73 m^2) and splenomegaly were noted. Urinalysis showed microhaematuria (31-40 Ec/HPF) and proteinuria (protein/creatinine ratio 50 mg/mmol). EBV serology was consistent with primary infection (IgM and IgG against EBV viral capsid antigen, negative EBNA). MPO-ANCA antibodies were positive at 101 U/mL. A renal biopsy demonstrated pauci-immune crescentic glomerulonephritis (11 fibrocellular and three cellular crescents in 57 glomeruli) and a mild interstitial infiltrate with isolated EBV-positive cells. We started immunosuppressive treatment with prednisolone and cyclophosphamide. Within a month, proteinuria decreased, the urinary sediment normalized and renal function improved, while lymphocytosis and EBV viremia also resolved.



Conclusions

Renal involvement ininfectious mononucleosis is uncommon and typically manifests as interstitial nephritis. In the reported case, EBV was responsible for splenomegaly and lymphocytosis, whereas the renal lesions were attributable to concomitant ANCA-associated vasculitis (AAV). The pathogenesis of AAV is incompletely understood but includes dysregulated autoantigen expression, exposure to related endogenous or exogenous antigens and B cell stimulation. While the temporal association of AAV with EBV primoinfection may be conincidental, it is tempting to speculate that EBV infection triggered autoimmunity. EBV stimuates B lymphocyte proliferation and has been shown in vitro to induce ANCA-production by B cells. Four cases of AAV associated with EBV primoinfection have been previously reported. These findings suggest a role of EBV in triggering AAV.

P 43

Sodium intake is associated with renal resistive index in an adult population-based study

David Jaques 1, Menno Pruijm 2, Daniel Ackermann 3, Bruno Vogt 4, Idris Guessous 5, Michel Burnier 6, Antoinette Pechère 1, Murielle Bochud 7, Belen Ponte 1

1. *Division of Nephrology, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland* ***2.*** *CHUV, Service de Néphrologie, Lausanne, Switzerland* ***3.*** *Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern and Department for BioMedical Research, University of Bern, Switzerland* , ***4.*** *Inselspital, Bern University Hospital, University of Bern, Department of Nephrology and Hypertension, Bern, Switzerland* ***5.*** *Division of Primary Care Medicine, Geneva University Hospitals, Geneva, Switzerland* ***6.*** *Nephrology and Hypertension Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland* ***7.*** *University Centre for General Medicine and Public Health, Lausanne, Switzerland*

Background

Renal resistive index (RRI) has been associated with adverse renal and cardiovascular outcomes. Although traditionally considered a marker of intrinsic renal damage, RRI could also reflect systemic vascular dysfunction. As sodium intake was linked to alterations in vascular properties, we wished to characterize the association of salt consumption with RRI in the general adult population.

Methods

Participants were recruited in a population-based study in Switzerland. RRI was measured by ultrasound in three segmental arteries. Sodium intake (UNa) (mmol/24h) was estimated on 24h urine samples. Carotidofemoral pulse wave velocity (PWV) was obtained by applanation tonometry. Mixed multivariate regression models were used with RRI or PWV as independent variables and UNa as dependent variable, adjusting for possible confounders.

Results

We included 1'002 patients in the analyses with 528 (52.7%) women and mean age of 47.2 +/- 17.4. Mean values of UNa and RRI were 141.8 +/- 61.1 mmol/24h and 63.8 +/- 5.5% respectively. In multivariate analysis, UNa was positively associated with RRI (p = 0.002), but not with PWV (p

= 0.344). Plasma renin activity and aldosterone did not modify the relationship between UNa and RRI (p = 0.087 for interaction). UNa/urinary potassium ratio was positively associated with PWV ≥12 m/s (p = 0.033).

Conclusions

Our results suggest that dietary salt consumption has a direct impact on renal hemodynamic in the adult general population. Alterations in vascular properties likely explain those findings, but inadequate renal vasomotor response is also possible. Sodium intake could thus potentially be linked to underlying structural systemic damages affecting this population.

Table 1: Patients characteristics according to tertiles of UNa (mmol/24h).

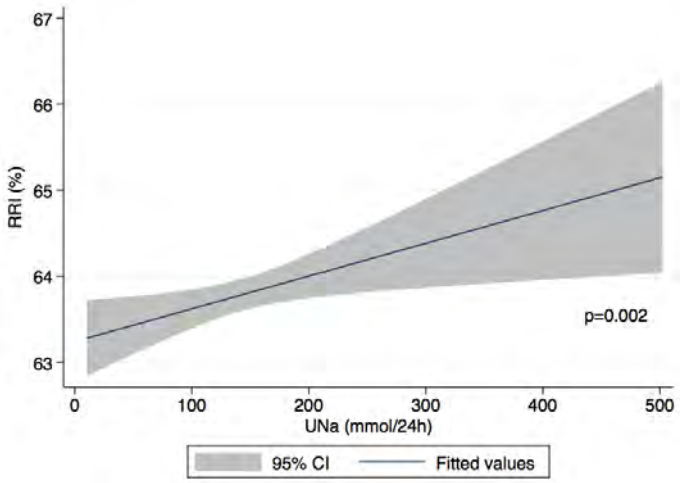
Characteristics	Overall N=1002	Low UNa (<110.4 mmol/24h) N=334	Medium UNa (110.4 – 160.5 mmol/24h) N=334	High UNa (>160.5 mmol/24h) N=334	p value
Categorical variables and comorbidities, n (%)					
Gender (female)	528 (52.7%)	237 (71.1%)	176 (52.6%)	115 (34.3%)	**<0.001**
Diabetes	39 (3.8%)	11 (3.2%)	15 (4.4%)	13 (3.8%)	0.726
Hypertension	228 (22.9%)	72 (21.8%)	74 (22.2%)	82 (24.5%)	0.678
Clinical characteristics, mean +/- SD or median (IQR)					
Age (years)	47.2 +/- 17.4	49.2 +/- 18	47 +/- 17.7	45.4 +/- 16.2	**0.019**
BMI (kg/m²)	25 +/- 4.5	24.2 +/- 4.6	25 +/- 4.4	26 +/- 4.4	**<0.001**
SBP (mmHg)	118.1 +/- 16.9	116.1 +/- 16.6	118.4 +/- 18	119.7 +/- 15.9	**0.017**
DBP (mmHg)	75.5 +/- 9.5	74.5 +/- 9.4	75.3 +/- 9.7	76.8 +/- 9.5	**0.008**
Laboratory characteristics, mean +/- SD or median (IQR)					
eGFR (ml/min/1.73m²)	96.5 +/- 17.9	93.5 +/- 18.5	96.9 +/- 17.9	99.2 +/- 17	**<0.001**
PRA‡ (ng/ml/h)	0.48 (0.24 – 0.76)	0.50 (0.24 – 0.84)	0.47 (0.24 – 0.74)	0.45 (0.24 – 0.71)	0.475
Aldosterone‡ (pg/ml)	60.7 (41.5 – 94.3)	68.7 (47 – 130)	62.5 (42 – 94.3)	54.5 (37 – 83)	**<0.001**
Urinary characteristics, mean +/- SD or median (IQR)					
UNa (mmol/24h)	141.8 +/- 61.1	81.6 +/- 22	134.9 +/- 13.9	209 +/- 48.4	**<0.001**
UK (mmol/24h)	63.7 +/- 23.1	53.7 +/- 21.3	63.1 +/- 18.5	74.4 +/- 24.4	**<0.001**
UNa/UK	2.1 (1.6 – 2.8)	1.6 (1.1 – 2.1)	2.1 (1.7 – 2.7)	2.8 (2.2 – 3.6)	**<0.001**
Urinary creatinine (mmol/24h)	12.7 +/- 4.2	10.6 +/- 3.2	12.6 +/- 3.5	15 +/- 4.4	**<0.001**
Urinary albumin (mg/24h)	5.9 (3.7 – 10.2)	5.8 (3.6 – 8.8)	5.9 (3.9 – 10.8)	6 (3.8 – 11.2)	0.204
Urinary volume (l/24h)	1.7 +/- 0.75	1.44 +/- 0.68	1.71 +/- 0.76	1.96 +/- 0.7	**<0.001**
Other relevant characteristics, mean +/- SD or median (IQR)					
RRI (%)	63.8 +/- 5.5	64.1 +/- 5.6	63.8 +/- 5.9	63.4 +/- 5.1	0.225
PWV (m/s)	7.4 (6.4 – 8.9)	7.5 (6.4 – 9.1)	7.3 (6.3 – 8.8)	7.5 (6.4 – 8.9)	0.668

‡: Available in a sub-group of 624 patients not treated for hypertension.
Abbreviations : PRA, plasma renin activity ; UK, urinary potassium ; PWV, pulse wave velocity.

Table 2: Factors associated with RRI (%) in final multivariate model.

Independent variables	Final model		
	β	95% CI	p value
UNa (mmol/24h)*	0.42	0.15; 0.68	**0.002**
Age (years)	0.11	0.09; 0.12	**<0.001**
Gender (women)	1.5	0.91; 2.08	**<0.001**
BMI (kg/m²)	0.11	0.05; 0.16	**<0.001**
SBP (mmHg)	0.12	0.11; 0.15	**<0.001**
DBP (mmHg)	-0.24	-0.27; -0.2	**<0.001**
HR (1/min)	-0.04	-0.06; -0.027	**<0.001**
Glucose (mmol/l)	0.73	0.38; 1.08	**<0.001**
Urinary creatinine (mmol/24h)	-0.1	-0.18; -0.02	**0.010**
Urinary volume (l/24h)	-0.52	-0.83; -0.21	**0.001**

*: Standardized to a mean of 0 and a SD of 1.
Model is also adjusted for age² and centre (not shown in the table).
Abbreviations: HR, heart rate.



P 44

Characteristics and outcome of pregnancies of women with chronic kidney disease in Switzerland - a single center perspective*

Fabienne Schmidli 1, Luigi Raio 2, Bruno Vogt 1, Laila-Yasmin Mani 1

1. Inselspital, Bern University Hospital, Department of Nephrology and Hypertension, University of Bern, Bern , 2. Inselspital, Bern University Hospital Bern, Department of Obstetrics and Gynecology, University of Bern, Bern

Background

Roughly 3% of women of reproductive age suffer from chronic kidney disease (CKD). Frequency of pregnancies among these patients is increasing. CKD and pregnancy mutually influence fetal and maternal outcomes. The purpose of this analysis was to study the characteristics and outcome of pregnancies with CKD of a single Swiss center and to identify determinants for obstetrical and renal short and long-term outcome.

Methods

In this retrospective cohort analysis 70 pregnancies in 70 adult patients were identified by chart review and analyzed according to pre-defined clinical parameters. Statistical analysis was performed using Excel software and included standard descriptive methods as well as student's t- and chi-square test to compare outcomes.

Results

Mean age at pregnancy was 32 years. Half of the patients were under nephrological care before pregnancy, the commonest disease entity being glomerulonephritis; two patients were transplant recipients; twelve patients received immunosuppressive therapy. At baseline, 80% of patients were in CKD stages 1-2, with proteinuria 0-1 g/d in 89% and a mean arterial blood pressure of 120.1/79.7 mmHg. One third of the pregnancies were first pregnancies, 6% realized after in vitro fertilization; in 29%, a hypertensive disorder of pregnancy (HDP) had been diagnosed during a preceding pregnancy. Low dose-acetylsalicylic acid was used in 55% of cases. HDP was diagnosed in 34% of patients, preterm delivery in 54% of patients (Table 1). New onset or permanent worsening of hypertension, of proteinuria or of renal function was noted in 6, 20 and 14 patients respectively. After a median follow up-time of 38.5 (0-298) months, 9% of patients had developed end-stage renal disease (Table 2-3). In univariate analysis, the main known risk factors for adverse obstetrical and renal outcome were confirmed.

Conclusions

This analysis gives insight into the characteristics and treatment practices of a Swiss single center cohort of pregnant patients with CKD.

* *Student paper*

Table 1: Pregnancy outcome

	number	mean/%	na
Hypertensive disorder of pregnancy	24	34%	0
Gestational Hypertension	2	3%	
Preeclampsia	16	23%	
Eclampsia	0	0%	
HELLP-Syndrome	6	9%	
Cesarean section	41	64%	6
Gestational week (mean)		34.11±7.07	7
Birth after 37 weeks	29	45%	5
Preterm delivery (< 37 weeks)	13	20%	5
Early preterm delivery (<34 weeks)	22	34%	5
Birth weight [g] (mean)		2332.6±942.9	10
Normal birth weight (≥ 2500g)	29	48%	10
Low birth weight (< 2500g)	18	30%	10
Very low birth weight (< 1500g)	13	22%	10
SGA (< 10th percentile)	14	23%	10
Admission to ICU	23	43%	16

Data are given as mean values ± standard deviation or as absolute values and proportions in relation to the total population. na = not available.

Table 2: Short- and long-term renal outcome

	Anzahl	%	NA
Episode of AKI (pregnancy - 3 months pp)	5	7	2
New-onset of chronic hypertension (> 6 weeks pp)	4	6	6
New-onset of microalbuminuria (> 3 months pp)	10	19	17
New-onset of proteinuria (> 3 months pp)	7	13	15
New-onset of renal dysfunction (> 6 months pp)	3	5	7
Permanent worsening of hypertension (> 6 weeks pp)	2	7	41
Permanent worsening of proteinuria (> 3 months pp)	10	36	42
Permanent worsening of renal function (> 6 weeks pp)	10	18	14
New-onset or permanent worsening of hypertension	6	-	-
New onset or permanent worsening of proteinuria	20	-	-
New onset or permanent worsening of renal dysfunction	14	-	-
Doubling of serum creatinine (pregnancy – las follow-up)	10	15	2
Development of ESRD (pregnancy – last follow-up)	6	9	1
Doubling of proteinuria (pregnancy – last follow-up)	14	54	44

AKI = acute kidney injury, pp = post partum, ESRD = end stage renal disease, na=not available. Data are given as absolute values and proportions in relation to the total population.

Table 3: Renal function before and after pregnancy

	Pre-Pregnancy	Post-Pregnancy	Last follow-up
Serum creatinine [µmol/l] (median, range)	74 (44-173)	76 (40-752)	87 (40-424)
eGFR CKD-EPI [ml/min/1.73m^2] (median, range)	90.2 (30.5-150-5)	86.25 (5.4-155)	73 (10.6-155)
Patients with proteinuria (number)	16	30	29
Proteinuria [g/d] (median, range)	0.0 (0 - 3.2)	0.26 (0 – 15.5)	0.0 (0 – 8.0)

eGFR=estimated glomerular filtration rate, CKD-EPI= chronic kidney disease epidemiology collaboration formula.

P 45

THE MANY FACES OF HYPERCALCEMIA: DIAGNOSTIC CHALLENGES IN CKD PATIENTS. A CASE REPORT*

Giovanni Giuliano 1, Bruno Vogt 2, Paola Rodoni-Cassis 3, Claudia Ferrier 4

1. University of Lausanne (Unil) , 2. Inselspital, Bern University Hospital, University of Bern, Department of Nephrology and Hypertension, Bern , 3. Clinica St. Anna, Lugano , 4. NefrocentroTicino

Background

Hypercalcemia may be the manifestation of various pathological disorders and can be associated with calciumphosphate metabolism imbalance. Primary hyperparathyroidism (PHPT) is characterised by high levels of PTH, hypercalcemia and low phosphatemia. In CKD-associated secondary hyperparathyroidism (SHPT), serum calcium is low and serum phosphate is elevated. Hypercalcemia may also be related to neoplastic disease, drugs and/or vitamin intoxication. PHPT, SHPT and/or other pathologies may all be present in CKD patients, which makes the diagnosis of hypercalcemia particularly challenging.

Methods

Case-Report: We report a case of a 80 year old Caucasian patient with H/O of arterial hypertension (HT), bipolar disorder and lithium-induced chronic renal failure (CRF) with eGFR of 30-37 ml/min/1.73 m^2 who presented with persistent hypercalcemia. Except for a treated HT, physical examination was unremarkable. His treatment consisted in lithium salts, 1,25-OH vit. D and a calcium antagonist.

Results

Initial laboratory data confirmed reduced renal function (creatinine 186 mmol/l, eGFR 29 ml/min/1.73 m^2), hypercalcemia (corrected calcium 2.66 mmol/l), normal phosphates (1.08 mmol/l), elevated iPTH (173.2 ng/l) and elevated alkaline phosphatase (191 U/l). Despite the interruption of lithium salts and 1,25-OH vit. D, hypercalcemia persisted. With further investigations a parathyroid adenoma was excluded by thyroid US, but a chest x-ray showed a pulmonary nodule in the superior right lobe, confirmed by CT-scan. After the diagnosis of nonmetastatic pulmonary adenocarcinoma, the patient underwent a right superior lobectomy. However, the hypercalcemia (2.69 mmol/l), of suspected paraneoplastic origin, persisted and was associated with normal phosphate levels (1.02 mmol/l) and elevated iPTH (202.7 ng/l). A parathyroid scintigraphy allowed the definitive diagnosis of a parathyroid adenoma on the trachea right side.

Conclusions

In CKD patients a differential diagnosis between PHPT and SHPT may not be straightforward. In the presence of hypercalcemia, normal-low phosphate and elevated PTH, an adenoma of the parathyroid gland should be ruled out.

**Student paper*

P 46

Acute kidney injury due to postrenal obstruction without hydronephrosis

Jakob Brune 1, Susanne Winkler 1, Patricia Hirt-Minkowski 1, Michael Dickenmann 1

1. *Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, Basel, Switzerland.*

Background

Although usually helpful in the assessment of acute kidney injury (AKI), laboratory tests and radiographic examinations can be misleading in individual cases. For example, the absence of hydronephrosis in diagnostic ultrasound imaging or computed tomography (CT) does not rule out post-renal AKI and “glomerular” proteinuria does not always indicate a glomerular damage.

Methods

We present a case report of a post-renal AKI where laboratory tests and radiographic examinations misled to invasive diagnostics and delayed final diagnosis and treatment.

Results

A 67- year old man with previously diagnosed urothelial cancer of the bladder presented with two consecutive

episodes of oliguric AKI within two weeks, both requiring short-term hemodialysis. Despite the absence of hydronephrosis in repeated ultrasound scans and one CT examination, there was a high pretest probability for postrenal obstruction. However, a first attempt to insert a nephrostomy failed. Nevertheless, kidney function improved spontaneously for two days. A kidney biopsy showed mild tubular damage with interstitial edema. While there was no significant proteinuria during the first episode, proteinuria of 5g/day with mostly “glomerular” proteins was detected during the second episode, leading to a second biopsy, which again showed no glomerular damage in accordance with the first biopsy. Due to the histological absence of glomerular damage we suggested a secretion of “glomerular” proteins by the tumor. Having no evidence for a pre- or intrarenal AKI, a bilateral nephrostomy was successfully placed in a second attempt. Renal function recovered completely within days and urine collected from the nephrostomy showed no more proteinuria.

Conclusions

The absence of hydronephrosis does not exclude urinary tract obstruction as a cause of AKI in high risk patients. Furthermore, secretion of proteins by a tumor can mimic “glomerular” proteinuria.

P 47

Evaluation of 24-h urine collection quality in the Swiss Kidney Stone Cohort - NCCR Kidney.CH *

Constance Legay 1, Daniel Fuster 2, Nasser A. Dhayat 2, Harald Seeger 3, Alexander Ritter 3, Thomas Ernandez 4, Catherine Stoermann-Chopard 4, Florian Buchkremer 5, Stephan Segerer 6, Grégoire Wuerzner 7, Sandra Schafroth 8, Tanja Haeusermann 8, Beat Roth 9, Carsten Wagner 10, Murielle Bochud 11, Olivier Bonny 12

1. *Department of Biomedical Sciences and Département épidémiologie et systèmes de santé, University of Lausanne and Unisanté, Lausanne, Switzerland* ***2.*** *Inselspital, Bern University Hospital, University of Bern, Department of Nephrology and Hypertension, Bern, Switzerland* ***3.*** *Universitätsspital Zürich, Klinik für Nephrologie, Zürich, Switzerland* ***4.*** *HUG, Néphrologie, Genève, Switzerland* ***5.*** *Kantonalspital Aarau, Nephrologie, Dialyse und Transplantation, Aarau, Switzerland* ***6.*** *Department of Nephrology, Dialysis and Transplantation, Kantonsspital Aarau, Switzerland ,* ***7.*** *Nephrology and Hypertension Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland* ***8.*** *NCCR Kidney.CH, Zurich, Switzerland* ***9.*** *CHUV, Service de Urologie, Lausanne, Switzerland* ***10.*** *Institute of Physiology, University of Zurich, Zurich, Switzerland* ***11.*** *Département épidémiologie et systèmes de santé, Unisanté, Lausanne, Switzerland* ***12.*** *Service of Nephrology and Hypertension, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland*

Background

Kidney stone affect one in ten adults in Switzerland. Diet plays a key role in the development and management of kidney stones. We collected data on the dietary habits of stone formers and controls using two consecutive 24-h dietary recalls and 24-h urine collections as well as blood chemistry. We explored the quality and completeness of 24-hour urine collections of participants prior to using 24-h urinary electrolytes and urea excretions as biomarkers of dietary intakes.

Methods

The Swiss Kidney Stone Cohort (SKSC) is a multicentric cohort of stone formers. A control group, free of kidney stone on CT-scan, was recruited in the general adult population. The SKSC includes 803 kidney stones formers and 207 controls (table 1). We evaluated the quality of the 24-h urine collection at baseline using urinary creatinine excretion (µmol/kg/24h). We also used a multiple linear regression model, including age, sex, BMI and linguistic region as covariates, to explore whether urinary volume and creatinine excretion differed between cases and controls.

	SKSC, n=803	Controls, n=207
Women, n (%)	256 (32%)	92 (45%)
Age (years), mean [min,max]	50.4 [18,90]	44.1 [20,86]
BMI (kg/m^2), mean (SD)	26.9 (4.9)	25.1 (4.4)

Table 1. Characteristics of participants to the Swiss Kidney Stone Cohort (SKSC) and control group.

Results

Of the 1882 urinary collections available, 631(33,5%) were outside the 10th-90th percentiles of the expected urinary creatinine excretion values. Mean 24-h urinary volume (day 1) was 1809±786ml (SKSC) and 2078±827ml (controls). After adjusting for age, sex, BMI and linguistic region, controls have a higher urinary volume than cases (+263±66ml, $p < 0.001$). Swiss Germans have higher urinary volumes (+153±52ml, $p < 0.01$). Adjusted mean 24-h urinary creatinine excretion (day 1) was similar in cases (164±52µmol/kg/24h) and controls (166±43µmol/kg/24h, $p = 0.6$).

Conclusions

The percentage of inadequate collections falls within a range previously described in the literature. Patients have lower 24-h urinary volume, but similar creatinine excretion than controls. Swiss Germans have higher urinary volumes. Further analysis will be conducted using 24-h urinary electrolytes (sodium, potassium) and urea excretions to assess the dietary intake of the participants.

* *Student paper*

P 48

Exercise-induced dissection of right renal artery - a rare cause of flank pain and microhematuria

Stephanie Damm 1, Nikolas Drivakos 1, Sarah Brunner 2, Markus Aschwanden 2, Patrizia Amico 3

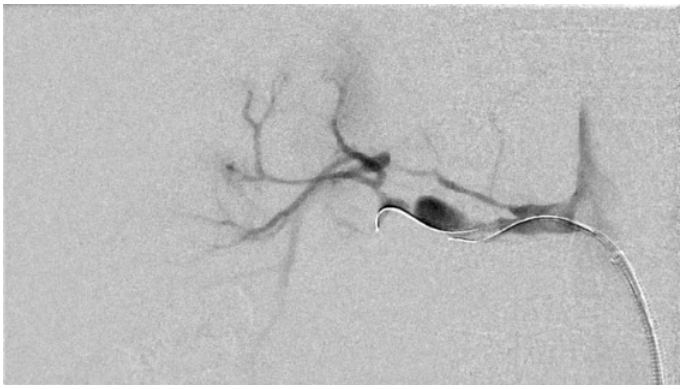
1. *Departement of Transplantationsimmunologie and Nephrology, University Hospital of Basel, Basel, Switzerland* ***2.*** *Departement of Angiologie, University Hospital of Basel, Basel, Switzerland* ***3.*** *Universitätsspital Basel, Transplantationsimmunologie und Nephrologie, Basel, Switzerland*

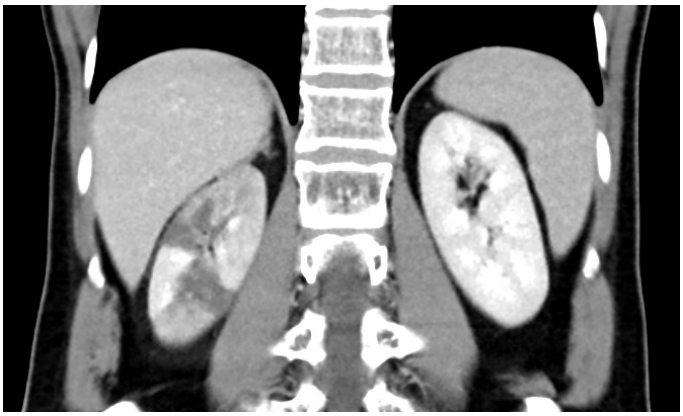
Background

Exercise induced dissection of renal artery is a rare cause of renal infarction necessitating high index of suspicion because the clinical presentation is non-specific.

Methods

A 30-year-old man witmarfanoid Habitus and no relevant medical history was seen at the A&E for right sided flank pain four days after weight lift training with microhematuria and normal renal function. Blood pressure and pulse were within normal range. He was suspected to have nephrolithiasis but neither a ct-scan of the abdomen nor a sonography revealed a calculus. He was discharged with analgesics but returned after two days with consistent pain. The localization of the pain in combination with an elevated lactat dehydrogenase raised (481 U/l) suspicion of a renal infraction and a ct-scan with contrast medium was performed.

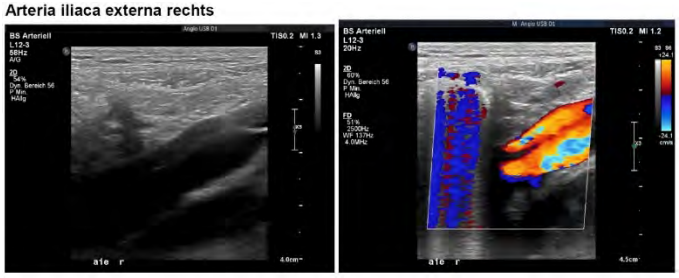




Results

The ct-scan showed a dissection/occlusion of a right polar renal artery with infarction as well as an asymptomatic dissection of the right external iliac artery. An evaluation of the thoracic and cranial blood vessels revealed no further dissection. Because of the stable renal function and the risk of further dissection no angioplasty of a coexisting ipsilateral high grade renal artery stenosis was performed initially. After one moth the renal function was declining without another etiology and an angioplasty was performed with stable renal function thereafter. Genetic testing for connective tissue disease was initiated but the result is still pending.

Arteria iliaca externa rechts



Conclusions

Exercise-induced renal artery dissection is a rare cause of renal infraction with male predominance, sometimes – as in our case – mimicing urolithiasis (1). Up to now there are only a few case reports in association with running(2), weight lifting (3) or sexual intercourse (4). A high clinical suspicion is needed to not miss the diagnosis.

1 Nakama, Acute Med Surg, 2020
2 Iqbal, Angiology, 2009
3 Braun, NDT Plus 2008
4 Elhassan, Int Med Case Rep, 2018

P 49

The Impact of the COVID-19 Pandemic on Hospitalization Trends for Acute Kidney Injury

Julija Voicehovska 1, Anda Grigāne 1, Baiba Adamaite 1, Eva Bormane 1, Georgijs Moisejevs 1, Dace Trumpika 1

1. *Riga East clinical university hospital, Kidney diseases and Kidney Replacement Therapy Clinics, Riga, Latvia*

Background

This study aimed to explore the effects of SARS-CoV-2 induced pandemia on the incidence of acute kidney injury (AKI) through analyzing hospitalizations with primary diagnosis of AKI.

Methods

We analyzed data from the Kidney diseases and Kidney Replacement Therapy Registry, Riga Eastclinical university hospital , Latvia, from March 2019-September 2019, compared to time period from March 2020-September 2020. Co-primary endpoints were AKI diagnosis and its cause, patients age, renal replacement therapy (RRT) and its modalities, namely, hemodyalysis (HD), continuous Veno-Venous Hemofiltration (CVVH), ultrafiltration (UF).

Results

In 2019, there were 105 patients diagnosed with AKI and required for RRT due to either clinical or biochemical indications. Distribution between age groups: 26% of age group above 75, 43% aged from 55 to 74 and 31% aged from 28 to 54. Among them, prevalence of such cause as hypertension and/or diabetes associated nepropathy was 39%, prevalence of sepsis-induced AKI was 48%, prevalence of AKI due to intoxication (etanol, medications) was 13%. The number of patients required HD accounted 38%, UF- 15%, CVVH - 47%. In 2020, there were 86 patients diagnosed with AKI. In terms of age groups, the patients aged above 75 compromised 23% of total, 55-74 years aged - 46%, 28 to 54- 31%. Among them, prevalence of hypertension and/or diabetes associated nepropathy was 48%, sepsis - 35%, intoxication (etanol, medications) was 17%. HD patients accounted 44%, UF -22%, CVVH- 34% of total accordingly.

Conclusions

During pandemia, the prevalence of arterial hypertension and diabetes associated AKI increased. This could be attributed to lack of primary care visits. Many patients are self-managed at home due to risk of exposure. We assumed, that arising number of etanol-induced intoxication is due to sedentary way of life, when people are more vulnarable, prone to psychoemotional stress.

No conflict of interest.

P 50

Hematuria and Klippel-Trenaunay syndrome: a uncommon cause

Bryan O'Callaghan 1, Sébastien Deglise 2, Olivier Phan 3

1. *Service de radiologie, HIB, Payerne, Switzerland* ***2.*** *Service de chirurgie vasculaire, CHUV, Lausanne, Switzerland* ***3.*** *Service de néphrologie, HIB, Payerne & CHUV, Lausanne, Switzerland*

Background

Klippel-Trenaunay syndrome can be caused by mutations in the PIK3CA gene and affects the development of blood vessels, soft tissues and bones. Malformations of veins can lead to internal bleeding from abnormal blood vessels. Here we report an uncommon cause of hematuria.

Methods

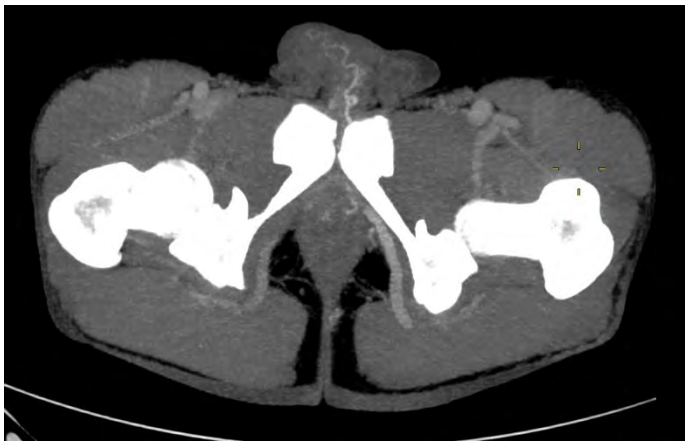
A 22-year-old patient was known for Von Klippel-Trenaunay syndrome, chronic renal failure (eGFR: 45ml / min / 1.73 m^2), several embolization of rectal arteries in 2005 due to recurrent rectal bleeding and crossectomy and stripping of the great saphenous vein in 2018. A 4 cm-lesion of the upper pole of the right kidney has been previously described on CT in 2009. For 3 weeks, he presented recurrent isolated total macrohematuria. On clinical examination, general condition was preserved, BP 156/89 mmHg, HR 76 / min, supple and painless renal compartments.

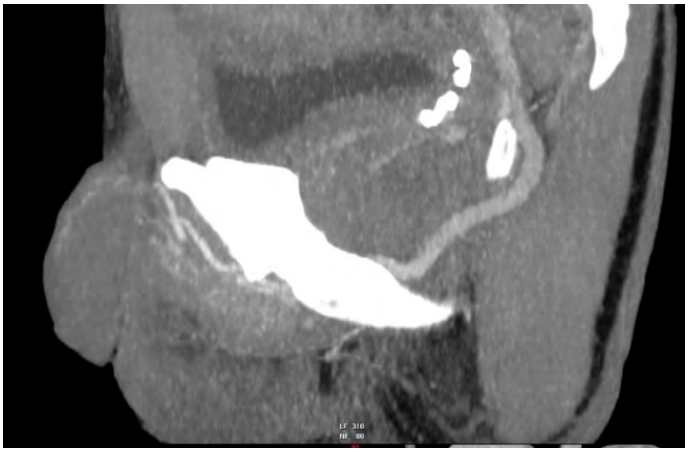
Results

A renal ultrasound revealed a 4 cm-heterogeneous lesion of the superior pole of the right kidney. No clots were seen in the bladder nor any vascular malformation in the bladder. An Angio-CT confirmed the lesion of the upper pole of the right kidney without evidence for abnormal vascularisation, suggesting the presence of an oncocytoma. Ectasia of the common and internal iliac arteries and veins were found as were severe ectasia of the left perineal veins extending into the penis.

Conclusions

In summary, we note the absence of vascular lesions in the bladder or kidney often found to be the cause of hematuria in Von Klippel-Trenaunay syndrome. We describe for the first time to our knowledge the presence of vascular ectasia in the penis that may explain the episodes of macrohematuria. A surgical evaluation should be needed to avoid further bleeding épisodes.





POSTER PRESENTATIONS – HEMODIALYSIS / PERITONEAL DIALYSIS

P 51

Use of glucagon-like peptide-1 receptor agonists (GLP1-RA) in dialysis patients

Stefan Pelz [1], Albin Schwarz [1], Patrice Ambühl [1]

1. Institute of Nephrology, City Hospital Waid and Triemli, Zurich, Switzerland

Background

Individuals with diabetes mellitus (DM) and with target organ damage, such as proteinuria or kidney failure (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2), are at very high risk to suffer death from cardiovascular complications. GLP1-RA have proven to reduce cardiovascular events, proteinuria and obesity in patients with DM. However, data of GLP1-RA treatment in dialysis patients is lacking. We report on our experience with a small number of dialysis patients, in which we initiated a treatment with GLP1-RA in order to assess its safety, tolerance and clinical outcome.

Methods

Semaglutide therapy once weekly was initiated in three of our hemodialysis patients and in one peritoneal dialysis patient, with a stepwise increase in dosage. All of them are patients with long duration of DM type 2, being on insulin. Primary outcomes were adverse effects from GLP1-RA (nausea, vomitin, gastrointestinal discomfort, pancreatitis) and weight loss. Secondary endpoint was reduction in HbA1c.

Results

Mean age was 62.3 years. Average weight when initiating GLP1-RA therapy was 108.3 kg, mean Body mass index (BMI) 29.6 kg/m^2. Semaglutide dose was increased in monthly steps according to the Plasma Glucose values. To date, none of the patients reported one of the adverse effects mentioned above and an average weight loss of 2.4 kg per Person (corresponding a BMI reduction of 0.9 kg/m^2) could be seen. Complete 6-months follow up data since start of GLP1-RA therapy will be presented at the congress.

Conclusions

The use of GLP1-RA in individual undergoing dialysis seems to be safe and a reduction in Body weight was found. Especially, patients on the waiting list for kidney transplantation might have an additional benefit from losing bodyweight, since obesity in this population has been associated with adverse outcome more frequently than in normal weight transplant recipients (wound infects, delayed graft function and graft failure.

P 52

Improving the Angiogenic Balance in Preeclampsia by Magnetic Blood Purification

Thomas Rduch [1], Inge K. Herrmann [2]

1. Swiss Federal Laboratories for Materials Science and Technology (Empa), Laboratory for Particles-Biology Interactions, Department of Materials Meet Life, Cantonal Hospital of St.Gallen Department of Gynecology and Obstetrics, St.Gallen, Switzerland 2. Swiss Federal Laboratories for Materials Science and Technology (Empa), Department of Materials Meet Life, Laboratory for Particles-Biology Interactions, St.Gallen, Switzerland

Background

Preeclampsia is a severe pregnancy associated disease affecting 3-8% of all pregnancies worldwide. Broadly defined by proteinuria (≥300 mg/24h) and hypertension. One crucial aspect of its pathophysiology is the antiangiogenic environment created by an excessive production of sFlt-1. With our work, we would like to explore a form of therapy that can alleviate the symptoms and thus prolong the pregnancy. We therefore sought to perform a feasibility study investigating the potential of magnetic separation based on removal of sFlt-1 from blood by an extracorporeal blood purification process based on magnetic separation.

Methods

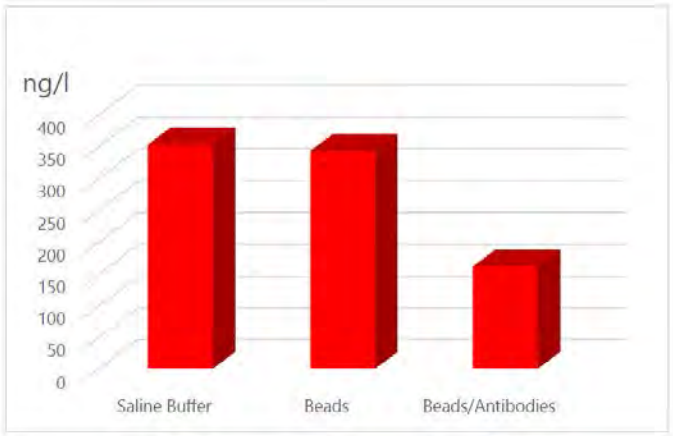
Magnetic nanobeads were functionalized with antibodies for sFlt-1. Blood samples from healthy volun-teers were spiked with recombinant sFlt-1 protein. The functionalized magnetic beads were applied to the blood samples and, after certain amount of time, removed by applying magnetic gradient field. The serum concentration of the remaining sFlt-1 was determined by ELISA and compared with samples which were treated with non-functionlized beads or saline buffer as negative control.

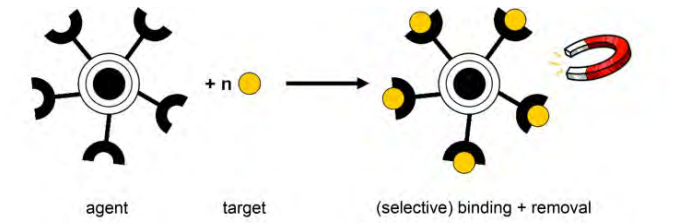
Results

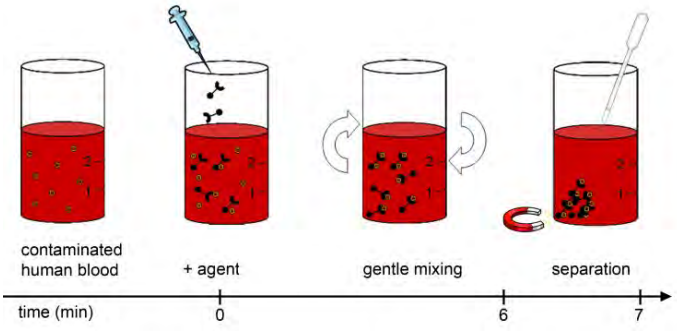
Nanobeads with a diameter of 300 nm and binding capacity of >300pmol/mg were functionalized with sFlt-1 antibodies. At a treatment time of 20 seconds, we could reduce the sFlt-1 concentration by 55%. (Initial concentration was 353 ng/l → after treatment 162 ng/l).

Conclusions

The blood purification, by removing sFlt-1 with functionalized nanobeads, is to a significant extent possible. Next steps will include the optimization of bead functionalization and contact time, the magnetic blood purification will be scaled up and carried out in continuous mode using a an extracorporeal blood purification circuit. Finally, the removal efficacy of the new magnetic blood purification approach will be compared to the clinical gold standard e.g. an dextran sulfat apharesis.







P 53

Survival on dialysis: Switzerland in comparison with other countries - A follow up

Rebecca Winzeler [1], Patrice Ambühl [1]

1. Institute of Nephrology, City Hospital Waid and Triemli, Zurich, Switzerland

Background

Survival in dialysis patients is substantially reduced compared to the general population. The aim of the present Analysis was to compare the survival of dialysis patients in Switzerland with other countries with an additional year of follow up and a higher number of patients.

Methods

Incident dialysis patients (hemo- or peritoneal dialysis; N = 5'406) from the Swiss dialysis registry were followed up from 2014 to December 31, 2019 (median follow up days = 658). Deaths occurring during this time (N = 1'353) were recorded and survival was examined using the Kaplan Meier method, censored for transplantation.

Results

Characteristics of the dialysis population stratified according to survival status are provided in Table 1. Dialysis patients in Switzerland have an approximately 8% higher survival in the first and second year and about 10% higher 5 years after start of dialysis, compared to other European countries (Annual ERA-EDTA Report 2017). In the first two years, the proportion in survival rates between genders is similar in Switzerland, as well as in Europe. After 5 years, however, a difference in survival rates between genders becomes apparent, with women having a 5-year survival probability of 56.6%, compared to a lower 5-year survival probability of 49.7% in men.

Conclusions

The markedly better survival in dialysis patients in Switzerland compared to other European countries could be confirmed with an additional year of follow up and more patients. Also, causes of death vary widely among European countries. 5-year survival was calculated for the first time, with Switzerland showing almost 10% better survival rates than other European countries.

Figure 1: Comparison of causes of death between hemodialysis patients in Switzerland and Europe (DOPPS)

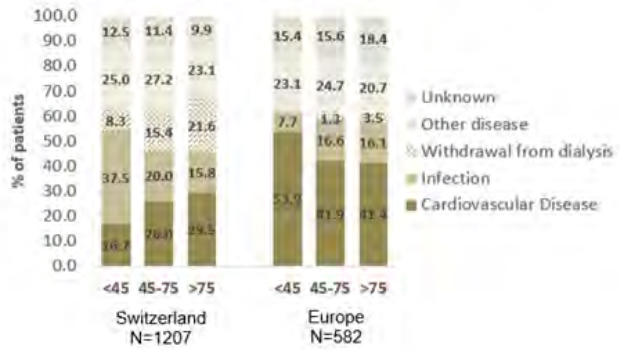


Table 1: Characteristics (given as mean±SD or percentage) in incident dialysis patients according to their survival status

	Non-Survivors, n=1'353	Survivors, n=4'053	
Age, years	74.2 ± 12.0	65.0 ± 16.4	0.000
Male gender, %	68.1	65.6	0.094
Body mass index, kg/m^2	24.5 ± 5.8	26.2 ± 5.6	0.000
Dialysis vintage, days	673 ± 479	810 ± 578	0.000
Dialysis duration, h per week	11.2 ± 1.5	11.5 ± 1.5	0.000
Kt/V	1.49 ± 0.40	1.59 ± 0.44	0.000
Hemoglobin, g/dL	10.5 ± 1.8	11.1 ± 1.4	0.000
Ferritin, ng/mL	568 ± 644	490 ± 405	0.000
Calcium, mmol/L	2.22 ± 0.23	2.22 ± 0.19	0.913
Phosphate, mmol/L	1.53 ± 0.50	1.63 ± 0.48	0.000
PTH, ng/L	300 ± 323	364 ± 311	0.000
Iron substitution, %	73.6	71.7	0.184
EPO substitution, %	82.1	80.0	0.114
Comorbidities, n	3.6 ± 2.1	2.1 ± 1.9	0.000
CCI*	6.0 ± 2.7	4.1 ± 2.1	0.000

Table 2: One-, two and 5-year survival probability (%) of incident dialysis patients, unadjusted, stratified by age, gender and cause of renal failure

		1 year		2 year		5 year	
		srrqap	ERA-EDTA	srrqap	ERA-EDTA	srrqap	ERA-EDTA
0-19 yrs	(N=59)	90.9	96.0	86.1	93.4	86.1	88.9
20-44 yrs	(N=450)	97.4	96.5	91.9	93.0	86.2	82.3
45-64 yrs	(N=1'467)	93.6	90.1	87.0	82.3	70.2	59.4
65-74 yrs	(N=1'419)	90.2	82.1	78.9	70.0	51.8	40.7
75+ yrs	(N=2'011)	87.6	72.8	74.5	57.0	39.4	23.9
Men	(N=3'579)	90.6	82.8	80.0	71.0	49.7	41.4
Women	(N=1'827)	90.7	82.7	80.5	71.6	56.6	43.7
Diabetes	(N=1'092)	90.2	84.0	79.3	71.2	45.6	38.7
Renal vascular disease	(N=1'244)	90.5	81.7	77.4	68.2	44.1	36.7
Glomerulonephritis	(N=809)	94.6	91.2	89.8	84.1	68.1	62.1
Other causes	(N=2'261)	89.5	81.1	78.9	70.3	55.1	43.4
All	(N=5'406)	90.7	82.8	80.1	71.2	51.8	42.2

P 54

Is icodextrin use feasible in peritoneal dialysis patient undergoing 18-FDG PET/CT scan?

Felix Burkhalter [1], Carla Hertel [2], Ineke Grendelmeier [1]

1. Division of Nephrology, University Clinic of Medicine, Kantonsspital Baselland, Switzerland 2. Transplant Immunology and Nephrology, University Hospital Basel, Basel, Switzerland

Background

18-FDG PET/CT scan is a useful diagnostic tool in patients with neoplasia or inflammatory diseases for further evaluation. Due to interference of glucose with the cellular uptake of the 18-FDG tracer via glucose transporter, withhold of any glucose source several hours before imaging is mandatory. This is also the case in peritoneal dialysis patients where glucose containing peritoneal dialysis fluid can't be used prior to 18-FDG PET/CT scan. Whether the same hold true for icodextrin is not known.

Methods

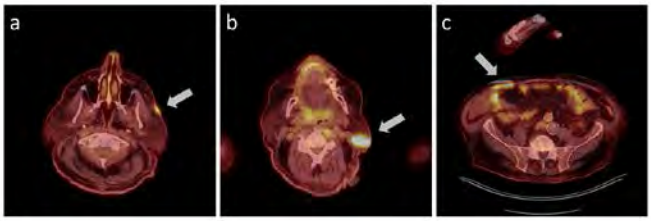
We describe two patients with metastatic carcinomas while on peritoneal dialysis, in whom icodextrin was used immediately before 18-FDG PET/CT scan

Results

In both cases 18-FDG PET/CT scan allowed the accurate diagnosis of metastatic lesions as well as in one case a simultaneous tunnel infection.

Conclusions

Our observation suggests that there is no significant interference of icodextrin with the metabolism of 18-FDG and so it is feasible to use icodextrin in peritoneal dialysis patients in case of 18-FDG PET/CT scan.



P 55

Demography of the dialysis population in Switzerland in 2019

Rebecca Winzeler [1], Patrice Ambühl [1]

1. Institute of Nephrology, City Hospital Waid and Triemli, Zurich, Switzerland

Background

The national Swiss Dialysis Registry (srrqap) has been established originally in the year 2006. However, participation is substantial only since 2013, when data collection became mandatory by law. The primary aim of the srrqap is to provide control and quality improvement for dialysis therapy in Switzerland. In the present analysis, select demographic characteristics of the dialysis population in Switzerland are given.

Methods

All medical establishments in Switzerland (both public and private; N = 94) providing chronic treatment by either hemo- and/or peritoneal dialysis, had to provide relevant data for the year 2019. All individuals being on chronic dialytic therapy in the year 2019 were enrolled (N = 4'704). For patients alive on December 31, 2019, data were gathered from this date or closest to this date. For patients who died during 2019 or were being transplanted, data refer to time of event, or to a date closest to the event.

Results

The mean and median age of dialysis patients in 2019 increased by 0.5 years compared to 2018. More than fifty percent of the patients were older than 71.8 years, and 1/4 were beyond 80 years. Female are less comorbid than male dialysis patients (4.16 vs. 4.65, p = 0.000), their dialysis vintage being higher than men's (53.7 vs. 45.1 months, p = 0.000) and they are older than male dialysis patients (69.3 vs. 68.6 years, p = 0.059)

Conclusions

With a coverage of 100% for both centers and patients, the data gathered can be considered highly representative. The incidence of dialysis therapy in Switzerland with 92.8 pmp is clearly lower than in most other European countries. In 2019, 3'844 prevalent patients (448.5 pmp) were dialyzed in Switzerland. The number of dialysis patients with diabetes increased again by 0.5% from 2018, reaching 37.8%.

Figure 1: Age trend for 2013-2019

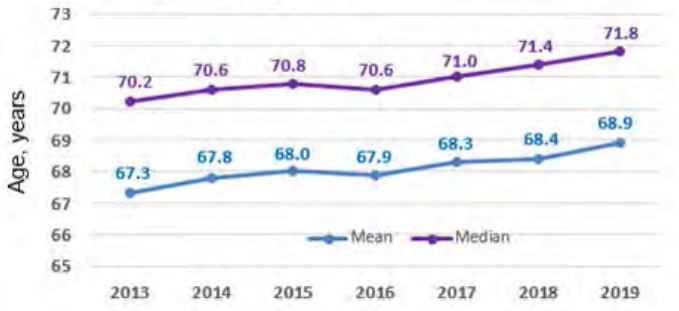


Table 1: Characteristics (given as mean and median) in dialysis patients

	All (100%)		In Centre (89.5%)		Home* (10.5%)	
	Mean	Median	Mean	Median	Mean	Median
Age, yr	68.9	71.8	69.2	72.5	62.8	66.0
Dialysis vintage, months	48.0	34.0	50.1	36.0	30.7	21.0
Comorbidities, N	2.6	2.0	2.7	2.0	1.9	1.0
Charlson Comorbidity Index	4.5	4.0	4.6	4.0	3.8	3.0
Hypertensive, %	83.2		82.9		86.0	
Sex (male), %	65.2		65.2		65.6	

Table 2: Trend of incident/prevalent count and comorbidities in dialysis patients from 2014-2019

	2014	2015	2016	2017	2018	2019
Total number of patients (cumulative)	4215	4453	4502	4580	4646	4704
Incidence, pmp	91.9	96.6	93.9	91.1	95.9	92.8
Prevalence, pmp	423.5	433.5	441.1	435.7	443.7	448.5
Comorbidities (mean), N	2.36	2.43	2.52	2.57	2.55	2.57
Charlson Comorbidity Index (mean)	4.44	4.42	4.49	4.51	4.49	4.48

P 56

Opioid use in swiss chronic hemodialysis patients: differences between an academic and peripheral dialysis center

Clémence Hennebel 1, Valérie Vilmont 1, Anne Cherpillod Grau 2, David Fumeaux 2, Fadi Fakhouri 1, Michel Burnier 1, Menno Pruijm 1

1. Nephrology and Hypertension Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland 2. Department of Nephrology, Hirslanden Clinique Cecil, Lausanne, Switzerland

Background

Pain is a common reported symptom in end-stage renal disease (ESRD) patients on chronic hemodialysis (HD). As NSAIDs are relatively contra-indicated, application of the WHO analgesic ladder theoretically leads to a more frequent use of opioids, but Swiss data are lacking. The aims of this study were therefore to assess the prevalence of opioid medication prescription and compare prescription patterns between an academic and peripheral dialysis center in Switzerland.

Methods

Prescription records and clinical characteristics were retrospectively retrieved from the medical records of all patients on HD since at least six months, and treated at Lausanne University Hospital (CHUV) or Clinique Cecil for the complete study period between September 2017 and September 2018. Informed consent was obtained from all participants.

Results

A total of 117 patients were included; 34 (29.1%) had a least one opioid prescription during the study period, and 9 (7.7%) were on chronic opioid prescription (>3 months). The two most commonly prescribed opioids were Tramadol (44.1%), and Buprenorphine (41.1%). Significantly more patients had received an opioid prescription at CHUV (27 out of 69 (39.1%), vs 7 out of 48 (14.6%) at Cecil, p = 0.004). This was partly explained by differences in comorbidities (see Figure). Pearson analysis showed that center (c = -0.26, P_V = 0.003), benzodiazepines (c = 0.21, P_V = 0.02), neuropathy (c = 0.23, P_V = 0.009) and amputation (c = 0.20, P_V = 0.02) correlated significantly with opioid prescription.

Conclusions

Our results showed that nearly a third of chronic HD patients had received at least one opioid prescription during the preceding year. Center was the best predictor of opioid use. The underlying reasons (differences in comorbidities and the number of prescribing doctors) for this center-difference need further study. These findings may increase the awareness to opioid prescription trends in HD patients and are a strong incentive to the elaboration of safety guidelines in pain management of HD patients.

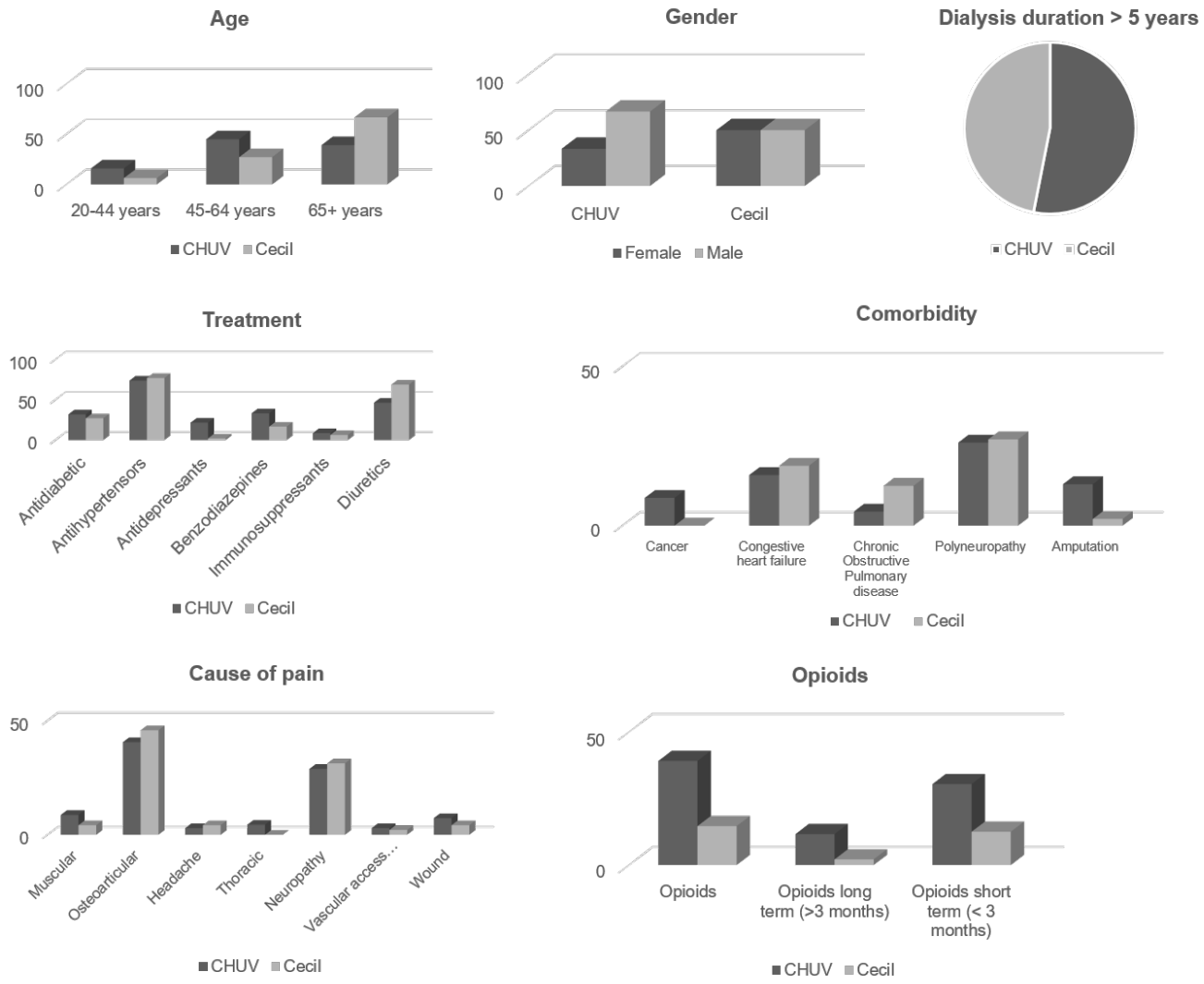


Figure 1. Characteristics of patients included at Lausanne and Cecil HD centers

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Swiss Medical Weekly
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CH-4132 Muttenz, Switzerland
Phone +41 61 467 85 55
office@smw.ch

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