SWISS NATIONAL CENTRE OF COMPETENCE IN RESEARCH

KIDNEY
CONTROL OF HOMEOSTASIS

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Kidney—Control of Homeostasis is a Swiss research initiative, headquartered at University of Zurich, which brings together leading specialists in experimental and clinical nephrology and physiology from the universities of Basel, Bern, Fribourg, Geneva, Lausanne, and Zurich, and corresponding university hospitals.

NCCR Kidney.CH
Institute of Physiology
University of Zurich
Winterthurerstrasse 190
8057 Zurich | Switzerland
Tel: +41 44 635 5216
Fax: +41 44 635 6814
www.nccr-kidney.ch
info@nccr-kidney.ch

SIDE EFFECTS OF CHRONIC KIDNEY DISEASE

Chronic Kidney Disease – a condition with multiple implications.

Renal diseases can accelerate the progress of cardiovascular diseases, significantly reducing life expectancy and leading to increasing medical costs. It is therefore important to further explore the reciprocal effect of chronic kidney and cardiovascular diseases.

Globally, an increasing number of people are suffering from chronic kidney disease (CKD), causing personal suffering and leading to rising costs for the healthcare system. The effects of renal disease are particularly serious, because they are closely related to cardiovascular disease. Current research shows that CKD plays an important role in the development of cardiovascular disease, which in turn further aggravates or accelerates the progression of kidney disease. This reciprocal effect is particularly noticeable in industrialised countries due to their higher life expectancy levels. However, despite evidence not only that cardiovascular mortality in CKD patients greatly exceeds levels in the general population but also that the majority of CKD patients die due to cardiovascular disease before they even reach end-stage renal disease, the medical community continues to underestimate the impact of CKD on cardiovascular disease.

UP TO 13 PER CENT SUFFER FROM CKD

CKD is defined as kidney damage or decreased kidney function (i.e. a decrease in the glomerular filtration rate (GFR)), which lasts more than three months. Kidney damage is generally diagnosed by imaging or the presence of albuminuria, commonly expressed as the urinary albumin to urinary creatinine ratio (ACR). For a decrease in GFR, a cut-off value of less than 60 ml/min is now widely accepted. Using this cut-off, about 11 to 13 per cent of the world's population have chronic kidney disease, with the majority of patients

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having GFRs between 30 and 59 ml/min (CKD stage 3). In people over 70, the chronic renal disease figure rises to 35 per cent.

Traditionally, it was assumed that CKD would inevitably progress. This progression is caused by intrarenal mechanisms (for example more rapid 'aging' of surviving nephrons and higher physical stress in the glomeruli due to the increase in filtration per surviving nephron) as well as systemic mechanisms such as hypertension and metabolic diseases like diabetes, obesity, phosphate toxicity and acidosis. However, better and earlier treatment of underlying diseases like diabetes and polycystic kidney disease as well as improved medical care with regard to hypertension and probably acidosis fortunately seem to stop the progression (these patients are labelled 'non-progressors') or even to improve kidney function—at least in well cared for CKD cohort populations. In cohorts of progressive CKD, the decline in GFR has recently been reduced to a little over 1 ml/min per year.

CONSEQUENCES OF THE LATE STAGES OF CKD

According to current research, the severity of CKD is closely related to a decrease in GFR. In severe impairment with GFR around or below 15 ml/min, increases in blood pressure are present and decreased renal erythropoietin (a growth factor for the production of red blood cells in the bone marrow) production will lead to anaemia, which will require treatment with recombinant hormone. In addition, the inability of the kidneys to eliminate acid leads to acid overload with increased respiratory work and decreases in bone and muscle masses, while the impairment of the elimination of potassium can lead to life-threatening cardiac arrhythmias. The metabolic intoxication caused by the accumulation of endogenous toxins that would normally be eliminated by the kidneys (among others ammonium and urea) is called uraemia. It causes nausea and vomiting and is characterised by various neuromuscular and central nervous system symptoms.

Effects on the cardiovascular systems of CKD patients are associated both with arterial disease and left ventricular hypertrophy (LVH)—a thickening of the muscle layers of the left heart chamber, which develops in up to 95 per cent CKD patients. LVH leads to a peculiar type of heart failure (stiff heart chambers), rhythm disturbances and sudden death.

In contrast to cholesterol-induced arterial disease, which affects the inner layers of the arteriae ('intima'), the changes in CKD primarily concern the muscle layer ('media'), which leads to wall stiffening and calcification. Uptake of phosphate via a phosphate-transport protein in vascular and cardiac smooth muscle cells is pivotal in initiating this life-threatening process. If phosphate overload is diagnosed by relying on the detection of an increased plasma phosphate concentration, arteriopathy and LVH are likely to be quite far advanced. The problem is that two phosphate eliminating hormones (osteocytic fibroblast growth factor 23 (FGF-23) and parathyroidal hormone (PTH)) increase long before the rise in plasma phosphate (see Figure) and are in fact homeostatic as they both stimulate the renal elimination of phosphate. Currently, some researchers are pursuing the possibility that LVH and arteriopathy are caused by this phosphate homeostatic response, notably the rise in FGF-23.

However, an alternative hypothesis defines CKD primarily as a Klotho-deficiency state. Healthy kidneys are the major source of Klotho, a protein that has important anti-ageing effects by inhibiting the ageing of the heart and the blood vessels. Novel scientific findings suggest that the cardiac and arterial diseases of CKD patients can be managed by using recombinant Klotho or a monoclonal antibody or small molecule inhibitors of the FGF-23 receptor. Clinical studies testing these hypotheses are underway.

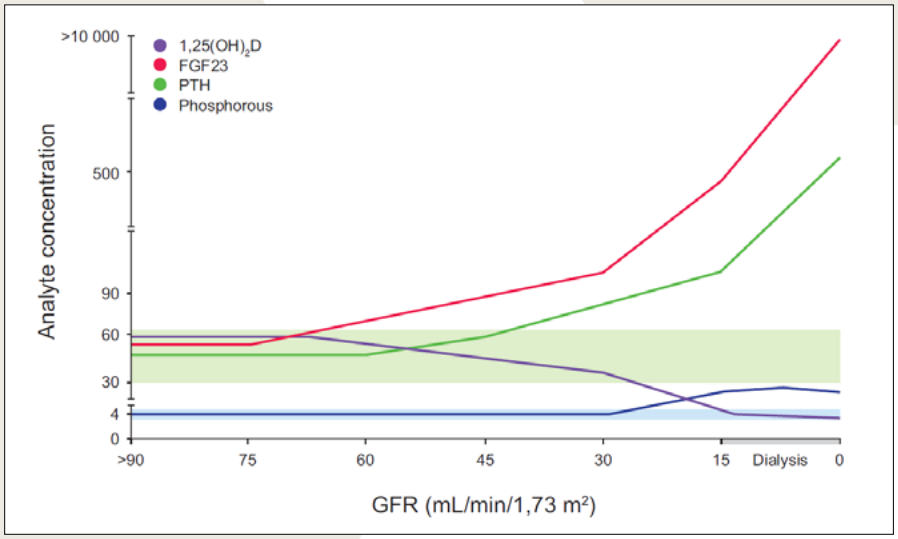
METABOLIC BONE DISEASE

It is not only cardiovascular diseases that are often CKD-induced, a certain metabolic bone disease (MBD) is also associated with CKD. Patients with MBD still exhibit only moderate decreases in renal function (GFR of 30-59 ml/min; i.e. CKD stage 3) and the bone disease is often only detected at a rather late stage. Nephrologists now consider this a disease in its own right (so-called CKD-MBD). MBD is a complex bone disease characterised by poor bone mineralisation, hyper-resorption of bone dictated by increased PTH, and low bone volume leading to fractures and bone pain. This metabolic bone disease is triggered because failing kidneys produce less bioactive vitamin D (1,25(OH)2D) and will gradually eliminate phosphate less and less efficiently. As a result, FGF-23 and PTH increase, which is also a consequence of Klotho deficiency (FGF-23, see Figure). Klotho is a co-receptor for FGF-23 and its absence results in renal resistance to FGF-23, explaining—at least in part—high FGF-23 levels. To treat CKD-MBD, dietary changes are strongly recommended, including lower phosphate intake, a replacement of vitamin D with vitamin D analogues and the oral administration of drugs that bind dietary phosphate, thereby reducing its intestinal absorption.

In summary, it is important to detect and treat cardiovascular and metabolic bone diseases already in the early stages of CKD. Otherwise they put patients at an increased risk of additional morbidity and even premature death and will also increase the economic burden caused by CKD.

Reto Krapf is a nephrologist and specialist in general internal medicine and works at the Hirslanden Klinik St. Anna in Lucerne. He is also Professor of Medicine at the University of Basel. His research focusses on the topic of putative phosphate toxicity in human subjects with normal renal function. Within the NCCR Kidney.CH he chairs, together with Professor Uyen-Huynh-Do, the Human Clinical Study Group.

Figure (green shaded area is the normal range for each parameter).



Prof. Dr. Michael O. Hengartner President of the University of Zurich and President of swissuniversities.

The University of Zurich is an internationally leading centre for life and health sciences. Organ and system physiology, in particular experimental kidney research, have a long and successful tradition in Zurich. As president of UZH, I am proud that my institution has been chosen as leading house of the National Center of Competence in Research Kidney.CH. The NCCR encompasses several major research programmes aimed at improving our understanding of kidney physiology and function in health and disease.

A major objective of both the NCCR Kidney.CH and of UZH is the application of new knowledge for the benefit of society. At the NCCR Kidney.CH, specialists in both experimental and clinical nephrology closely collaborate in order to accelerate the translation of pre-clinical findings into new treatments. In this way, the NCCR Kidney.CH not only contributes substantially to strengthening the position of Switzerland as a hub for medicine and life sciences, but it also enhances future medical care in our country. I congratulate the NCCR Kidney.CH on the great work that they have done so far and very much look forward to the further development of this important initiative!

Prof. Dr. Michael O. Hengartner

BALANCING FAMILY AND A SCIENTIFIC CAREER

Joana Delgado Martins and David Penton Ribas want it all: A scientific career as researchers plus the life of a young family, with their nine-month-old daughter Camila. Both are aware that it won't always be easy to balance their professional and personal lives, but after all, they've overcome other challenges before. David came to Europe as a doctoral student in 2008, his wife Joana moved—in 2008—from Portugal to Germany to continue her PhD at the University of Regensburg. In 2014 they came to Zurich together, where they both managed to receive funding through the European IKPP programme and to find new positions as postdocs at the University of Zurich (UZH). With their research in the groups of Andrew Hall and Johannes Loffing, respectively—both members of the NCCR Kidney.CH and professors at the university's Institute of Anatomy—Joana and David are exploring the mechanisms of kidney function in health and disease. With the support of the NCCR Kidney.CH they also hope to tackle this new challenge as a family of three.

WHAT HAS CHANGED IN YOUR LIVES SINCE YOUR DAUGHTER WAS BORN?

Joana: We now need to plan every single day very carefully to be able to make progress in our projects while still spending some quality time together and with our daughter. Achieving the so-called work–life balance is easier said than done.

IS IT HARDER FOR WOMEN THAN FOR MEN?

David: I guess it depends on how much help they get from their partner. For us, it's easy to understand each other's professional challenges since they're the same for both of us.

DAVID, HOW DO WOMEN AND MEN COMBINE JOB AND FAMILY IN YOUR HOME COUNTRY, CUBA?

David: In Cuba, maternity leave is longer than in Switzerland and day care, although of lower quality, is largely subsidised by the state. Moreover, the support one gets from one's parents is crucial. It's difficult to generalise, but at least in my family it was always common that both partners pursued their own careers and contributed to raising the kids.

JOANA, DID YOU EVER CONSIDER TAKING A BREAK FROM YOUR PROFESSIONAL CAREER?

Joana: Yes. At the beginning it was difficult to leave our daughter in day care. But I received a lot of support from David and we both decided to keep pursuing our careers.

HOW DOES YOUR HUSBAND SUPPORT YOU?

Joana: We try to share family and household duties equally. When one of us has a deadline, the other one takes care of our daughter. We also alternate at home when she's sick. As we both work in the same field, we also get input from each other concerning projects and results.

WHAT KIND OF SUPPORT DO YOU RECEIVE FROM OTHERS?

Joana: Both UZH and the NCCR contribute to our day care expenses. Camila goes to a day care centre that belongs to the kihz Foundation (Kinderbetreuung im Hochschulraum Zürich). It isn't far from the university and many of the other parents are in a similar situation. Our colleagues in the lab are also very understanding if we have to adjust meeting times or need to leave the lab at a certain time to pick up our daughter.

HOW HAVE YOUR CAREERS PROGRESSED SINCE YOU CAME TO SWITZERLAND?

David: We both received IKPP2 support, were integrated in a network of the world's leading scientists in the field and gained a lot of visibility by participating in various meetings in Switzerland and abroad. We also have access to significant research resources that enable us to successfully develop our projects.

HOW HAS THE NCCR BEEN INSTRUMENTAL TO YOUR PROGRESS?

David: The NCCR has been essential in supporting our research, not only financially but also in terms of networking, education and even in our family project.

WHAT ARE YOUR NEXT OBJECTIVES?

Joana: We are both trying to publish relevant papers in our fields and are aiming to become independent investigators. In addition, David is currently pursuing his 'habilitation' at the UZH Medical Faculty.

WHAT ARE YOUR SPECIAL RESEARCH INTERESTS?

David: Joana is interested in deciphering the cellular signalling pathways involved in the pathophysiology of the proximal tubule of the kidney nephron.
Joana: And David wants to better understand the renal regulation of salt homeostasis and blood pressure.

THE NCCR KIDNEY.CH RETREAT 2017 – INTENSIVE DAYS IN MURTEN

All members of the NCCR Kidney.CH were welcomed to the 7th Retreat on February 9, 2017 with an aperitif and dinner at the SBB Centre Loewenberg in Murten—a much appreciated opening to an intensive gathering the following day. More than 80 participants enjoyed networking and exchanging the research results of all the work packages of Kidney.CH. Christine Ziegler, an invited external guest from the University of Regensburg, gave a talk on the field of structural biology ('Role of lipids in transporter and channel regulation'), provided attendees with very interesting insights into her career path and shared her experiences as a female scientist. The other external guest, Ruedi Aebersold from ETH Zurich, complemented the programme with insights into new strategies in proteomic research and introduced briefly the Swiss Personalized Health Network and the increasing significance of 'big data' in medical science.

POSTER AWARD 2017

From Left to Right: Director François Verrey, Claus-Dieter Schuh and Vice-Director Johannes Loffing

At the Retreat 2017, 50 posters were presented during two poster sessions. The three best posters were selected by a jury consisting of members of the NCCR's Steering Committee and Advisory Board. The directors of Kidney.CH—François Verrey and Johannes Loffing—awarded first prize to Claus-Dieter Schuh (postdoc in the Hall lab, UZH). The second prize went to Nourdine Faresse (Junior Grant awardee from 2013, UZH), and Faik Imeri (postdoc in the Wenger lab, UZH) received third prize.

5TH E-LEARNING MODULE COMPLETED – CAS/DAS IN TRANSLATIONAL NEPHROLOGY

15 young scientists from the NCCR Kidney.CH network have passed the 5th and final module of the e-learning series on Translational Nephrology with good to excellent results. All participants who passed all five modules will receive a Certificate of Advanced Studies (CAS) in Translational Nephrology from the University of Bern.

Module 5 on "Metabolism and Chronic Kidney Disease" had started in autumn 2016 and ended with the return session on March 2, 2017 in Bern. During the course, the participants had to review online resources and to complete various questionnaires. In addition, they studied annotated articles individually and took part in several group assignments. As final task, the students worked both individually as well as in small groups on a clinical case. The series of e-learning modules has started anew on March 3, 2017 with a kick-off meeting for the 1st module on "Salt and Water Transport". During the meeting the following lectures were held: Jean-Pierre Montani, University of Fribourg, talked about "A Guytonian view of sodium homeostasis and blood pressure control", Johannes Loffing, University of Zurich, about "The renal distal tubule – Key player for the control of salt and water homeostasis", and Bernard Rossier, University of Lausanne, focused on "Case Base learning «About sodium and water»".

More information about the CAS/DAS education programme "Translational Nephrology": www.nephrologie.unibe.ch

RESULTS OF THE 5TH HCP CALL

On February 11, 2017 the NCCR Kidney.CH's Steering Committee approved five proposals for human/clinical and translational cooperative projects (HCP). This call has been extended for pilot studies and tool developments, which will have impact on the 3rd phase of the NCCR Kidney.CH.

Approved HCP projects (Main applicant / Project title)

Olivier Devuyst (UZH): Uromodulin and kidney stone propensity: Studies in the Swiss Kidney Stone Cohort

Johannes Loffing (UZH): Generation of novel antibodies against total and phosphorylated NCC, alpha-ENaC, and Klotho and their experimental validation in Gitelman patients

Thomas Müller (USZ): Dynamic measurement of renal functional reserve as a predictor of long-term renal function

David Hoogewijs (UniFr): Novel Epo regulating transcription factors

Eric Feraille (UniGe): Generation and characterization the kidney tubule-specific DTR-expressing mice to generate a new tubular CKD model

EVENTS

MINISYMPOSIUM: REDEFINING NEPHROLOGY – WHAT'S HOT, WHAT'S NEW?
June 22, 2017
Kleiner Hörsaal Ost USZ, Zurich, Switzerland

50TH ESPN ANNUAL MEETING
September 6—9, 2017
Glasgow, UK

9. JAHRESTAGUNG DER DEUTSCHEN GESELLSCHAFT FÜR NEPHROLOGIE
September 14—17, 2017
Mannheim, Germany

ASN ANNUAL MEETING 2017
Oct 31 – Nov 5, 2017
New Orleans, LA, USA

49TH ANNUAL MEETING OF THE SWISS SOCIETY OF NEPHROLOGY
December 7—8, 2017
Fribourg, Switzerland

55TH ERA-EDTA CONGRESS
May 24—27, 2018
Copenhagen, Denmark

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