SWISS NATIONAL CENTRE OF COMPETENCE IN RESEARCH

KIDNEY
CONTROL OF HOMEOSTASIS

NEWSLETTER ::: NO. 8 ::: JUNE 2014

Kidney – Control of Homeostasis is a Swiss research initiative, headquartered at University of Zurich, bringing together leading specialists in experimental and clinical nephrology and physiology from the Universities of Basel, Berne, Fribourg, Geneva, Lausanne and Zurich, and corresponding University Hospitals.

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CALCIFICATION – HOW TO IMPROVE KIDNEY PATIENTS' LIFE EXPECTANCIES

Glyfada Cave near Pyrgos Dirou, Mani Peninsula, Peloponnese

Many kidney patients don't live long. Although there are many individual exceptions to this rule, overall there has been only marginal improvement to this depressing fact over recent decades. Accelerated vascular calcifcations appear to be a major cause. So once again the centuries old statement of English physician Thomas Sydenham (1624–1689) seems to be proven true: 'A man is as old as his arteries'.

CONSEQUENCES OF CALCIFICATION

But why is there accelerated calcification of the vessels of kidney patients and how does it lead to death? On a very basic level, vascular calcification is a consequence of the dysregulation of mineral homeostasis which occurs when kidney function deteriorates. This leads to an impaired renal excretion and, therefore, to calcium and phosphate accumulating in the body. These are the major constituents of the mineral apatite, which forms the main mineral component of physiologic (bone and tooth) as well as pathologic (soft tissue, blood vessels) calcifications. Why then do patients die from calcifications? When blood vessels calcify, the initially elastic arteries get stiffer and stiffer over time, until there are only a rigid tubes left. Today's reading is that this imposes a major burden on the heart, which has to pump against an increasingly growing resistance. You cannot live with this condition for very long.

TODAY'S THERAPEUTIC APPROACH

Given these considerations, it is prudent to try to prevent high calcium and phosphate levels in renal patients. This is what is done in clinical practice today. However, clear evidence is still lacking that this approach prolongs life. But why? Everything has been so logical up to this point...

EXPANDING THE VIEW

Looking at calcium and phosphate only is most likely not enough. As it turns out, we have for a long time neglected other important aspects. Even in healthy

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EDITORIAL

Francois Verrey is a professor at the Institute of Physiology of the University of Zurich and Director of the NCCR Kidney.CH

With elan towards its second phase

The NCCR Kidney – Control of Homeostasis is starting its second four-year phase: time to look back and to move forward. During its first phase, Kidney.CH created a strong community of researchers involving departments and nephrology clinics at all Swiss universities with medical faculties. Thanks to the support of the Swiss National Science Foundation and the University of Zurich, our four collaborative research modules were able to generate significant novel results that would not have been possible without this nationwide network. Importantly a new clinical study group has been created that aims to coordinate and organize joint projects among Swiss nephrology centres (e.g. the Swiss kidney-stone cohort). Yet another strengthening of Swiss kidney-related research was achieved with the creation of new professorships. Furthermore, by providing modern teaching in renal pathophysiology, Kidney.CH strongly fosters the education of the next generation of kidney researchers. During its second phase the research of our NCCR will focus on kidneys as regulators and targets for oxygen, dietary elements, ions, and calcifications, using basic research approaches and involving translation from bench to bedside and back to the bench. We shall also continue to strive to enhance awareness of the central role played by the kidneys for homeostasis control in health and disease.

François Verrey
Director Kidney.CH

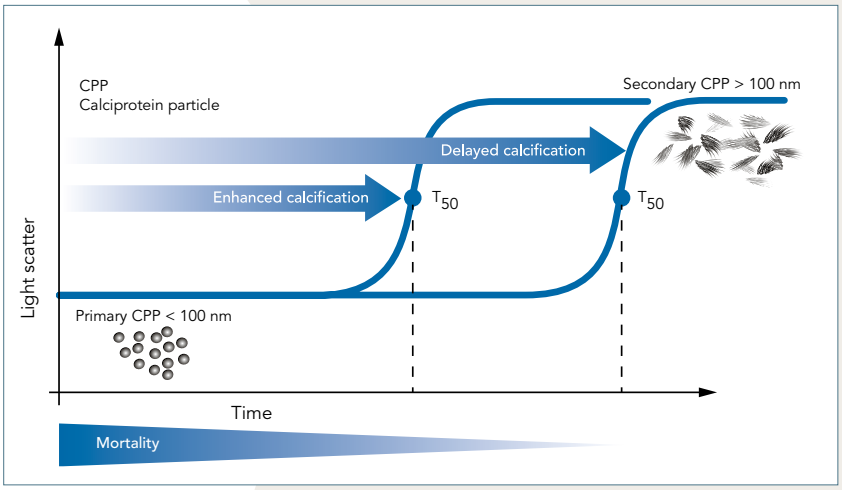
individuals, most body fluids are supersaturated with calcium and phosphate. If these were the only determinants, virtually everybody would calcify over the years. But nature has found an efficient manner of preventing this. A system of calcification inhibitors and promoters are present in body fluids and tissues to regulate where calcification should occur (bones and teeth) and where not (soft tissue and blood vessels). And it is becoming increasingly clear that not only too much of calcium and phosphate induces pathological calcifications, but also a lack of calcification inhibitors.

DECIPHERING THE CODE

The interplay between all these factors, many already known, but many still to be identified, establishes a system of calcification regulation. When concentrations of calcium and phosphate rise, this system binds surplus molecules and arrests them in a loose, precrystalline, so-called amorphous state. Fetuin-A, the strongest calcification inhibiting protein in blood, is specially equipped to bind high amounts of calcium and phosphate. In the blood of kidney patients clusters of Fetuin-A molecules have been found, which form nanosize calciprotein particles (CPP). Small calcification inhibitor molecules (e.g. pyrophosphate and magnesium) further stabilize these complexes.

NEW INSIGHTS AND OPPORTUNITIES

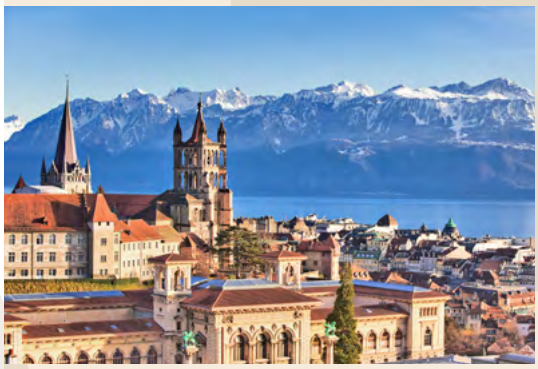
So there is increasing evidence for the existence of a regulated system of calcification inhibition and promotion. The challenge now is to characterize how this system works in detail, and how it causes dysregulations in kidney patients.
A very valuable in vitro method for analyzing the functional activity of this system has recently been



In vitro method for analyzing the functional activity of the spontaneous transformation of primary CPPs, which contain amorphous calcium phosphate, into secondary CPPs, which contain crystalline calcium phosphate.

PORTRAIT LAUSANNE

HYPERTENSION WITH A GRAIN OF SALT



Hypertension affects about 30% of the population and is one of the main risk factors worldwide for cardiovascular diseases (CVD), heart attacks, and strokes.

Blood pressure is mainly determined by the renal control of sodium balance and by the renin-angiotensin-aldosterone system, and a large proportion of hypertensive patients respond favourably to a reduction of salt intake. For more than 30 years, Lausanne has been leading basic and clinical research in salt-sensitive hypertension, contributing to decisive breakthroughs in the fight against this widespread condition.
Two men and their teams have placed Lausanne at the forefront of research in this area. The men in question are Bernard Rossier and Hans Brunner. Rossier deciphered the role of aldosterone in the distal nephron and cloned its main effector, the epithelial sodium channel (ENaC). ENaC is the apical sodium conductance identified in the distal convoluted/connecting tubules of the nephron and in the collecting duct and is the target of the diuretic drug amiloride. Rossier and his team demonstrated ENaC's role in two mirror human monogenic diseases causing a severe form of hypertension in Liddle's syndrome and a salt-losing syndrome in pseudohypoaldosteronism type 1 thus establishing ENaC as the ultimate regulator of sodium homeostasis.

POTENTIAL TREATMENT METHODS

They also proposed a new way of regulating transport channels by the activation of cascades of proteases, which provide new potential opportunities for treatment. Rossier created an active and productive core of renal basic research in Lausanne and established transgenic animal models of hypertension (in

developed by the author of this article, and its research application is supported by the NCCR Kidney.CH. This method monitors the timing of the spontaneous transformation of primary CPPs, which contain amorphous calcium phosphate, into secondary CPPs, which contain crystalline calcium phosphate. The high-throughput set-up of the test makes it possible to analyze the effects of inhibitory and promotiv substances. Furthermore, CPPs can be artificially generated using patient blood and their composition and interaction with cells can be analyzed.

BEYOND THE IVORY TOWER

This method can also be used to quantitate the calcification regulation system in individual patients. With a few droplets of blood, information is obtained regarding the functional calcification propensity of serum, that is to say – the integrated activities of all calcification inhibitors and promoters compressed into a single laboratory value.

This method is a major step forward. Not only has it been shown to correlate with calcification progression, but also to predict the survival of kidney patients. In this aspect it is a better biomarker than any other lab value used today.

Developing this novel blood test for routine clinical care is the aim of Calcisco Ltd., a start-up company co-led by Matthias Meier, the former scientific project manager of the NCCR Kidney.CH and by the author of this article (see also box). There is hope, that the research of the NCCR Kidney.CH and the broad availability of this blood test will eventually provide a basis for improving the survival rate and ameliorating the suffering of kidney patients.

CALCISCO – GETTING THE KNOWLEDGE TO THE PATIENT

Calcisco Ltd., a Swiss start-up company, is developing and marketing the novel and unique blood calcification test mentioned in the cover story, for use in clinical routine practice. Its co-founders are Dr Andreas Pasch, a researcher at the NCCR, Prof. Willi Jahnen-Dechent from RWTH Aachen, Germany an expert in basic research on biomineralization, and Matthias Meier, former scientific project manager of the NCCR Kidney.CH. The start of this tech-transfer-story 'from bench to bedside' has been promising: Calcisco has won two of the most prestigious start-up competitions – the Heuberger Winterthur Jungunternehmerpreis and all stages of the venture kick competition – and has been nominated for the de Vigier entrepreneur prize. Its own labs have been established within the central lab facilities of University Hospital Bern, Inselspital. A first routine test offer shall already be established by the end of 2014.

Calcisco Ltd.
Founded:
August 2013
Headquartered:
Bern, Switzerland
Founders:
Dr Andreas Pasch
Matthias Meier
Prof. Willi Jahnen-Dechent
Employees:
5
Business area:
Development and marketing of an in vitro diagnostic test for the early detection of calcification propensity in human blood

Andreas Pasch
CEO & co-founder of Calcisco Ltd. and research group leader at the Department of Nephrology, Hypertonia and Clinical Pharmacology of Inselspital Bern and associated participant within the NCCR Kidney.CH.

Matthias Meier
CEO & co-founder of Calcisco Ltd. and former scientific project manager of the NCCR Kidney.CH.

collaboration with Edith Hummler). In addition, he brought together experts in cellular biology, physiology, biochemistry, and electrophysiology (Olivier Staub, Laurent Schild, Jean-Daniel Horisberger, Käthi Geering, and Dmitri Firsov among others), who developed new tools and extended the research interest to the whole kidney and beyond.

NEW TRANSGENIC TECHNOLOGY

Several members of this team are now involved in the NCCR programme Kidney.CH, further dissecting the interactions between sodium reabsorption and potassium secretion in the kidney and between the sodium co-transporter NCC and ENaC. The programme also allowed the successful implementation of a new transgenic technology called TALEN. This was used to establish rat knock-in models targeting the mineralocorticoid and the glucocorticoid receptors.

Hans Brunner became a pioneer in the treatment of hypertension by targeting the renin-angiotensin-aldosterone system. He built a strong and internationally recognized team (Michel Burnier, Bernard Waeber, Daniel Hayoz, Thierry Pedrazzini, Juerg Nussberger, Marc Maillard and Eric Grouzmann). This team covers all basic and pharmacological aspects of treating hypertension with inhibitors of the angiotensin-converting enzyme (ACEI) and antagonists of the angiotensin 2 receptors (ARA). Both ACEI and ARA have since been largely used in the clinic, and are among the most frequently prescribed drugs worldwide.

Michel Burnier, Chairman of the Service of Nephrology and Hypertension of Lausanne University Hospital, is today still developing translational research in this field. He attracted several promising young investigators to the field and participated in the creation of a clinical research center with a focus on human research in hypertension. He also started a fruitful collaboration with the epidemiogeneticist Murielle Bochud who leads several populational cohorts (including the Swiss Salt Study, SKIPOGH, and partially CoLaus). Together, they promoted several initiatives dedicated to reducing salt consumption in the Swiss population.

Decisive assets of the kidney research carried out in Lausanne are its strong basic aspect as well as its application of the latest molecular and transgenic technologies to human physiological studies and even to epidemiological and interventional trials, in order to carry on the fight against hypertension and renal and vascular diseases. Collaboration between people and teams and within the NCCR Kidney.CH network is expected to raise research to the highest level of excellence and to impact positively on patients' conditions.

Olivier Bonny
is an assistant professor at the Department of Pharmacology and Toxicology of the University of Lausanne and associated participant within the NCCR Kidney.CH

IMPRESSIONS FROM THE KIDNEY.CH RETREAT 2014

The retreat in February 2014 was one of the highlights of the events organized by the NCCR Kidney.CH. Seventy participants travelled to Loewenberg Centre in Murten to intensively exchange current research results and ideas during the two-day retreat. The poster session with over forty posters offered a great opportunity for discussing and learning more about novel approaches and exciting findings. Lisa Crowther's poster was selected by an NCCR jury as winner of this year's poster award.






POSITIVE FEEDBACK FOR SECOND KIDNEY.CH E-LEARNING MODULE

The second Kidney.CH e-learning module was successfully completed in March 2014. The module had been developed and implemented in autumn 2013 after the first module on 'salt & water' had proved to be a major success.

The second course focused on 'acid & base' handling of the kidney and on associated diseases that occur when this balance is disturbed. Kick-off for the module took place in October 2013 and included presentations on 'Acid-base homeostasis: a view on transporters, metabolic pathways, and sensors' (Carsten Wagner, University of Zurich) and the 'Clinical evaluation of acid-base disorders' (Nilufar Mohebbi, University Hospital of Zurich). In the following weeks, groups of four to six participants explored the topic based on six annotated articles and the information available via an online platform.

In March 2014, all groups met with their tutors, four Kidney.CH experts, for a presentation and discussion of their work. Feedback on the course both from tutors and participants was very positive. The final quiz of participants confirmed that the objectives had been achieved and all passed with top grades. The next e-learning module will be on calcium/phosphate handling and is planned to start in the last quarter of this year.

NEWS FROM THE KIDNEY.CH MANAGEMENT OFFICE: GOODBYE MATTHIAS – WELCOME JENS!


Matthias Meier


Jens Selige

Matthias Meier receives our heartfelt thanks for his efforts and commitment as scientific project manager at the NCCR Kidney.CH throughout its first four years. He had already joined the NCCR before its official launch in summer 2010. Thanks to his extensive experience with biotech companies and his background as a biologist, his know-how was a very valuable addition to our academic expertise. With his enthusiasm, sense of organization, fairness, and humour, he has played a central role in shaping our NCCR and in strengthening both our internal and our external communication. His strong commitment to technology transfer is one of the reasons he is now leaving us to create a new Swiss biotech start-up company (Calcisco, page 3). We wish him every success in this venture.

With Matthias departing, we are happy to welcome Jens Selige as our new Kidney.CH scientific project manager. He brings with him a broad and complementary background with a diploma in Biotechnology (Berlin and Montpellier) and a PhD from the University of Konstanz. He previously worked for the pharmaceutical company Altana Pharma AG / Nycomed GmbH and gathered extensive experience as scientific coordinator for the University of Konstanz and for SystemsX.ch, the Swiss initiative in systems biology at the ETH Zurich.

We are very fortunate to have found in Jens an excellent new scientific project manager to start the second phase of our NCCR, and warmly welcome Jens to the programme.

François Verrey and Jan Loffing

EVENTS

6. JAHRESTAGUNG DER DEUTSCHEN GESELLSCHAFT FÜR NEPHROLOGIE
September 6–9, 2014
Berlin, Germany

47TH ESPN ANNUAL SCIENTIFIC MEETING
September 18–20, 2014
Porto, Portugal

ASN-KIDNEY WEEK
November 11–16, 2014
Philadelphia, PA, USA

46TH ANNUAL MEETING OF THE SWISS SOCIETY OF NEPHROLOGY
December 4–5, 2014
Interlaken, Switzerland

52ND ERA-EDTA CONGRESS
May 28–31, 2015
London, UK

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University of Zurich[UZH]

FNSNF
Swiss National Science Foundation