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, Berne, Fribourg, Geneva, Lausanne, and Zurich, and corresponding university hospitals.

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WHAT WE EAT… OR THE IMPACT OF OUR DIET ON OUR KIDNEYS

A treat with consequences: The Western diet can be a major health risk.

What we eat has a significant impact on the functioning of our kidneys. New research projects at the NCCR Kidney.CH are therefore examining how Western diet influences the onset and development of chronic kidney diseases.

Maintaining the balance—or homeostasis—within our bodies is a prerequisite for health. Kidneys play a central role in this. Every day the kidneys filter and selectively reabsorb nearly 200 litres of liquid from the blood to control the volume of body fluid and its salt and nutrient content. In addition, kidneys excrete waste products, and are involved in the regulation of red blood cell production, blood pressure, glucose metabolism, bone density and much more.

KIDNEY DISEASE AND ITS MAIN CAUSES

Chronic kidney disease represents an increasingly heavy burden on our society. For one, kidney diseases lead in the long run to renal failure, which requires expensive and often unsatisfactory replacement therapy. But even at an earlier stage, alterations in the functioning of our kidneys cause frequent and devastating disorders such as arteriosclerosis and osteoporosis. Thus, preventing kidney diseases is of great importance.

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Pierre-Yves Martin is Professor of Nephrology and head of the Department of Nephrology at Geneva University Hospitals (HUG)

'What should I eat and drink to protect my kidneys?'
This is one of the first question a nephrologist needs to answer when meeting a patient with chronic kidney disease. After all, kidneys are the organs that eliminate the toxic and waste end-products of the body's metabolism. However, this is also one of the most difficult questions to answer.
Over the last two decades various dietary issues have been shown to impact the progression of chronic kidney disease (CKD). These include the amount of water intake, sodium control, protein restriction, acid reduction, potassium limitation, phosphates avoidance, antioxidants... And the list is still growing, which confirms the importance of diet in CKD management.
Since so many dietary factors can impact a patient's health many nephrologists will feel uncomfortable advising patients on diet. Meanwhile a lot of patients will find it hard to follow extensive dietary recommendations. Therefore clinicians and researchers need to redouble their efforts to better outline the role of dietary interventions in CKD progression. This will help physicians and patients to implement dietary changes.
One of the objectives of the 5th International Kidney.CH Symposium will be to better determine dietary impact. The event will be a superb opportunity to discuss challenges in diet and CKD with a panel of outstanding speakers.

Pierre-Yves Martin

Two well-known causes of chronic kidney disease are arterial hypertension and diabetes. In both cases, diet plays a central role in the onset and development of the disease. But dietary habits also impact the functioning of the kidneys independently of hypertension and diabetes, and may—themselves—cause kidney disease.

THE CHALLENGE OF FOOD

Each meal is a major challenge for maintaining the homeostasis within our bodies and the kidneys have to quickly adapt their excretory function to our dietary intake. The beneficial and adverse effects of certain diets on human health and disease are well documented. Our Western-type diet, especially, is frequently considered to be a major health risk. It is characterized by a high intake of increased amounts of red and/or processed meat, high-fat foods, refined grains, sugary desserts and high-sugar soft drinks. Thereby it contrasts with most traditional diets, which contain substantial amounts of fruit, vegetables and wholegrain foods, and less meat. Specifically, the Standard American Diet (similar to the Western-type diet) consists of 50% carbohydrate, 15% protein, and 35% fat – values that exceed the dietary guidelines for fat and animal proteins. And this Western meat-sweet diet is a nutritional habit being adopted by many people in developed and increasingly also in developing countries.

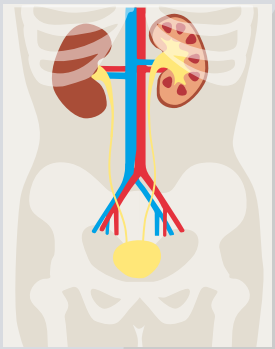
The adverse impact of the Western diet is usually attributed to its effects on the cardiovascular system, neuro-hormonal regulation, and fat deposition, and thereby indirectly also on renal function. It is becoming increasingly clear that our food intake may also directly influence renal health and the progression of kidney disease. However, we still know little about underlying cellular and molecular mechanisms and important questions remain largely unaddressed: Is it possible to attribute certain deleterious effects more precisely to specific dietary components? Can we prevent, reduce or halt chronic kidney disease's progression by specific dietary measures? Are there scientific rationales for such recommendations?

EXAMINING THE IMPACT OF WESTERN DIET

The 'Dietary Impact' work package of the NCCR Kidney.CH addresses these questions and examines the impact of Western diet components—in particular phosphate, protein and salt—on chronic kidney diseases. For example salt consumption (sodium chloride) is not only important in relation to blood pressure regulation. Transporting sodium chloride back from the filtered primary urine into the extracellular space (blood) is—in energy terms—the most costly task of the kidneys. It interferes directly and indirectly with the reabsorption of water and other solutes, and also impacts on inflammatory conditions. Dietary salt levels therefore play a complex role that needs to be investigated more accurately.

Calcium phosphate metabolism controls a very important and delicate equilibrium that allows the body to form a very solid skeleton containing calcium phosphate hydroxyapatite crystals. This metabolism also assures that no pathological calcium phosphate crystals can form in the kidneys or elsewhere in the body. This complex equilibrium is controlled to a large extent by a number of hormones and factors that regulate the balance of calcium and phosphate. Because of the complexity of this system, highly controlled studies with human subjects need to be performed to better understand the interaction of dietary phosphate with therapeutic interventions such as—for instance—a treatment with the hormone vitamin D3.

PROGRESSION OF CHRONIC KIDNEY DISEASE (CKD)



WESTERN-TYPE DIET
HIGH-FAT, HIGH-PROTEIN,
HIGH-PHOSPHATE, HIGH-SALT

HYPERTENSION

DIABETES

HEALTHY KIDNEYS

CHRONIC KIDNEY DISEASE (CKD)
KIDNEY FAILURE
KIDNEY REPLACEMENT THERAPY

Too much nutritional protein has been shown to negatively impact on the kidneys, in particular when their function is already altered. This deleterious effect has been proposed to be mediated by an overstimulation of the kidney filtration rate and also by the surplus acid load that animal proteins represent. As the mechanisms involved are not yet fully understood it is a cause for concern that—alongside a protein-rich diet—amino acids, which are the building blocks of proteins, like arginine and leucine are additionally promoted as healthy food supplements. Therefore, preclinical studies are currently investigating whether this type of treatment does have negative effects on the kidneys.

BETTER NUTRITIONAL RECOMMENDATIONS

The studies are taking into consideration that all these dietary components are per se essential. However too much of them could be deleterious to health. For each there could be an optimal range of intake which varies depending on the person and the progression of a chronic kidney disease. Thus, like the famous Swiss German renaissance physician Paracelsus (1493-1541) noted: 'The dose makes the poison'. The research aims at increasing our understanding of the beneficial and adverse impact of Western diets on kidneys and shall pave the way towards better nutritional recommendations.

François Verrey
is Professor at the Institute of Physiology of the University of Zurich, member of the Zurich Center for Integrative Human Physiology (ZIHP), and Director of the NCCR Kidney.CH

PORTRAIT: WORK PACKAGE 3—ION BALANCE

HOW OUR FOOD LEADS TO HIGH BLOOD PRESSURE

Sodium, potassium and phosphate in our food profoundly affect our arterial blood pressure. Cellular and molecular mechanisms in the kidneys seem to play a central role. These mechanism are now being explored.

Arterial hypertension affects more than 1 billion people worldwide. It is one of the leading causes of atherosclerosis and its complications—myocardial infarction, stroke and renal failure. Therefore it is important to understand the mechanism in question:

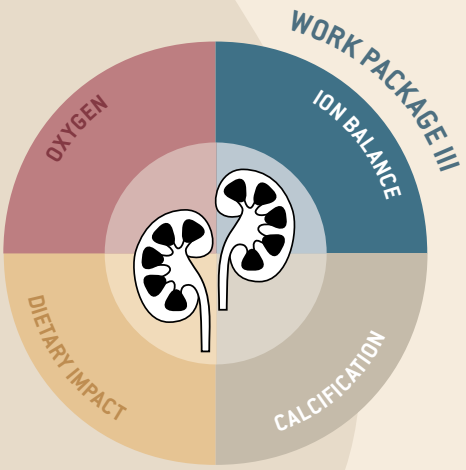
The control of arterial blood pressure is complex and involves both genetic and environmental factors. Dietary intake of ions seems to play an especially major role. Our modern diets are usually rather high in sodium (Na^+) and inorganic phosphate (P_i) but low in potassium (K^+) compared with the natural, unprocessed food eaten by our ancestors. It is becoming increasingly clear that our modern eating habits contribute to the high prevalence of hypertension.

A high intake of sodium increases the risk of hypertension, while potassium has antihypertensive effects. This has been emphasized by the recent PURE study, which analyzed data from more than 100,000 adults from a total of 18 countries (N Engl J Med 371: 601–611; 2014). In addition, inorganic phosphate could also impact blood pressure as data from recent animal models suggests (EMBO Mol Med 6: 744–59; 2014).

From the seminal work of American physiologist Arthur Guyton, we know that kidneys and their tubular salt handling are critical for blood pressure control. As long as the kidneys are healthy they are able to maintain homeostasis and blood pressure even over wide ranges of altered ion intake. The kidneys perform this job with astonishing accuracy despite the numerous solutes and huge amounts of fluids that need to be handled in parallel. However, even small imbalances in the involved signalling and transport processes may cause the system to deteriorate.

In the NCCR's work package 3, groups from Zurich (Loffing and Wagner) and Lausanne (Staub and Hummler) teamed up to elucidate the cellular and molecular mechanisms by which the kidneys adapt their functioning to altered ion intake and how this contributes to the control of homeostasis and also blood pressure. The research focuses on potassium and inorganic phosphate. Experiments in cell lines, animal models, and human probands address fundamental questions such as: How does the body notice altered ion intake? How is this information (e.g. from the gut) transmitted to the kidney? Are direct ion sensing mechanisms of renal epithelial cells involved? Which signal transduction mechanisms contribute?

In cooperation with Murielle Bochud of Lausanne, who leads the NCCR's 'population genetics platform' (newsletter No. 9), we are also investigating the possible association of blood pressure salt-sensitivity with genetic loci and thus aim to identify genetic pre-depositions for the sensitivity of blood pressure to altered ion intake in the general population.



Johannes Loffing
is an MD and Professor of Anatomy at the University of Zurich. He is vice-director of the NCCR Kidney.CH and is responsible for the super-vision of the NCCR's educational programme and for its gender-equality measures. Moreover, he heads the imaging and microscopy platform and coordinates the research projects in work package 3 (WP3) 'Ion Balance'.
He is an expert in kidney histology and specializes in the structural and functional analysis of renal functions. His particular interest concerns the functions of the renal distal convoluted tubule (DCT). The DCT is the main target for thiazide-diuretics and plays an important role in blood pressure control. Within WP3, Loffing contributes to projects that address the role of dietary potassium (K^+) in the regulation of renal functions. In this context, his team recently showed that an enhanced dietary K^+ intake rapidly shuts off the thiazide-sensitive NaCl co-transporter in the DCT, which may contribute to the antihypertensive effect of a K^+ rich diet.

THIRD KIDNEY.CH E-LEARNING MODULE COMPLETED

The third e-learning module focused on calcium and phosphate homeostasis. It had begun in autumn 2014 and ended on March 12, 2015 in Bern. This year's exams consisted of three components. The students needed to present annotated scientific articles to one of three tutors (Olivier Bonny, Andreas Pasch, or Spyridon Arampatzis). Students also had to pass two online quizes that focused on the online resources made available by the online platform of the International Fellowship Programme on Integrative Kidney Physiology and Pathophysiology (IKPP).

A total of 18 young scientists from the Kidney.CH network completed module 3. They achieved good to excellent grades—ranging from 4.9 to 6 points—in their final scores. The NCCR again received positive to very positive feedback on its e-learning module. The few critical remarks made will be taken into account to further improve the e-learning platform.

E-learning module number 4 is now under construction and will focus on oxygen sensing. The kick-off meeting for this module will be held in October 2015 at the University in Bern.

RETREAT 2015: EXCHANGE OF EXPERIENCE

The annual NCCR Kidney.CH retreat took place in February and was held, just like in previous years, at the SBB Loewenberg Centre in Murten. During the two-day event over 80 participants took the opportunity to get to know other scientists from the NCCR's network and to learn more about their research.

The keynote speaker of the retreat was Howard Riezman from the University of Geneva. In his speech he gave interesting insights into the activities of the NCCR Chemical Biology. Another main topic of the event was "Knowledge and Technology Transfer". The Institut für Jungunternehmen, the Swiss Commission for Technology and Innovation (KTI)—represented by Philip Hassler and Peter Harboe-Schmidt—and Matthias Meier from Calcisco AG talked about their experience with start-up companies.

About 40 posters were presented at the poster session. They covered topics from all fields of research at the NCCR Kidney.CH. The NCCR's jury selected the poster of Jan Czogalla, postdoc from the Loffing Lab, as winner of this year's poster award (more pictures at www.nccr-kidney.ch).

RESULTS OF THE 1ST HCP CALL

The NCCR's jury—consisting of its Advisory Board and members of the Steering Committee—in February approved six proposals for human/clinical and translational cooperative projects (HCP).

The first call for proposals met with much interest. Genome-wide association studies (GWAS), especially, were regarded as a valuable addition to existing NCCR Kidney.CH research projects.

Overview of Approved HCP Projects
(Main applicant/Project title)

Roland Wenger: Heritability of RBC and Epo traits: towards the identification of novel Epo regulatory factors and functions

Carsten Wagner: Identification of genes associated with serum phosphate and renal phosphate handling

Edith Hummler: Identification and confirmation of candidate genes responsible for potassium sensitivity of blood pressure (unbiased screening approach)

Andreas Pasch: Calcification propensity score in the SKIPOGH cohorts I and II, followed by clinical correlations and GWAS

Murielle Bochud: Genome-wide association studies for selected kidney-related phenotypes

Nilufar Mohebbi: The effect of dietary phosphate intake on blood pressure regulation and renal sodium chloride excretion in healthy male volunteers

2ND CALL FOR PROPOSALS:

A second HCP call was launched in March. The submission deadline for proposals is August 31, 2015.

EVENTS

48TH ESPN ANNUAL MEETING
September 3–5, 2015
Brussels, Belgium
www.espn-2015.org

7. JAHRESTAGUNG DER DEUTSCHEN GESELLSCHAFT FÜR NEPHROLOGIE
September 12–15, 2015
Berlin, Germany
www.nephrologie2015.aey-congresse.de/

RENAL WEEK
33RD ANNUAL ISBP MEETING
September 18–19, 2015
St. Petersburg, Russia
www.renalweek2015.org

ASN KIDNEY WEEK 2015
November 3–8, 2015
San Diego, CA, USA
www.asn-online.org/education/kidneyweek/

47TH ANNUAL MEETING OF THE SWISS SOCIETY OF NEPHROLOGY
December 3–4, 2015
Basel, Switzerland
www.swissnephrology.ch

53RD ERA-EDTA CONGRESS
May 21–24, 2016
Vienna, Austria
www.era-edta2016.org

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