It is an enormous honor for me to have been elected as a President of the ERA-EDTA!

It is the first time that an ERA-EDTA President comes from Eastern Europe (after Prof. Horst Klinkmann from Eastern Germany; 1987-1990) and this is certainly a sign that our Society has really become a truly full European Society.

Growing interest worldwide

During the Presidency of my predecessor, Professor Raymond Vanholder, ERA-EDTA developed several new projects and collaborations that go outside of Europe, showing how the interest on our initiatives has grown worldwide, and how our efforts are appreciated.

Some of these initiatives are unique and, therefore, ERA-EDTA has been ahead of its time: we now have a very well established, and I may add very active, Young Nephrologists’ Platform; we have one of the most transparent “Declaration of Interest” forms regarding potential conflicts of interest for not only committee members, but also speakers at all our events; we are now starting a fruitful collaboration with DOPPS (as an EUROPOPPS initiative) and with The Lancet – just to mention some of them.

During my term I would like to continue these activities started during the recent years but I would also like to pay more attention to European matters of ERA-EDTA, with special focus on Central and Eastern European countries. A stricter and more rational system for financial expenditures, and new rules for CME courses in European countries and countries surrounding the Mediterranean Sea will be introduced.

Support for younger colleagues

I would like to support our younger colleagues, providing them with several encouraging offers to become ERA-EDTA members. It is also essential to improve the lobbying activities for kidney issues within the European Parliament and European Commission (through the European Kidney Health Alliance of which ERA-EDTA is a full member). Finally, I will especially focus on the collaboration with our Registry (there is its 50th anniversary this year), our Working Groups, the ERA-EDTA endorsed working groups and ERBP. We must not forget the importance of the activities of our Scientific Advisory Board with several ongoing and new projects.

Social media: helpful tools

New technologies can significantly increase the interaction with and among our members. Also our public relations require constant adaptation to the fast changing world. Our profiles in the social media, our website, the role and structure of our journals: all these should be a helpful tool to activate and attract more members. It is also essential to improve the lobbying activities for kidney issues within the European Parliament and European Commission (through the European Kidney Health Alliance of which ERA-EDTA is a full member).

Finally, I will especially focus on the collaboration with our Registry (there is its 50th anniversary this year), our Working Groups, the ERA-EDTA endorsed working groups and ERBP. We must not forget the importance of the activities of our Scientific Advisory Board with several ongoing and new projects.

I hope to be able to continue in the excellent way in which ERA-EDTA is going, with the help and support of my fellow colleagues, but I can also say, true friends of the ERA-EDTA Council and also with the entire staff of our Headquarters in Parma.
It all started here!

At the opening ceremony, the historical role of Amsterdam for the ERA-EDTA was celebrated.

The opening ceremony on Friday evening marked the official start of the 51st ERA-EDTA Annual Meeting. In his welcome address Congress President Pieter ter Wee stressed the historical role of Amsterdam for the ERA-EDTA; after the society was founded in 1964, the city hosted its first annual meeting, which started with 82 participants. 50 years later the ERA-EDTA Annual Meeting has grown into the largest nephrology meeting in Europe. More than 8,000 attendees not only from Europe but also from America, Asia and the Arab countries, are expected this year. 2013 was actually an excellent year for the society with the largest membership growth in its history, according to Raymond Vanholder, whose term as President of the ERA-EDTA will end with this congress. The Society’s positive development is reflected in various scientific projects and collaborations that have been initiated over the last years. Moreover, the ERA-EDTA Awards, which were handed over during the opening ceremony, are convincing evidence of the excellent scientific work done by society members.

At the society’s first congress in Amsterdam, an important decision was taken: the creation of a registry of all European patients on replacement therapy for renal failure. The registry Registry became a unique example of international cooperation. Since June 2000, the Registry office is housed in the Department of Medical Informatics in the Academic Medical Center in Amsterdam. Today it includes core data on the demography, renal disease, treatment and outcomes of half a million RRT patients. This huge amount of data makes it a forerunner in the field of renal epidemiology. However, collecting data is not just a goal in itself. Christoph Wanner, Chairman of the ERA-EDTA Registry and Council Officer, stresses the importance of close collaboration between the Registry and ERA-EDTA workings groups, as well as various cohorts and consortia.

Space medicine – a future topic for nephrologists?

The management of water on earth and water resources in the universe were the key topics of the opening lectures on Friday night. Bernard Foing, ESA Chief Scientist, took his audience on a fascinating trip to the planets of our solar system: in his overview, Foing went through the evidence for liquid water on Mars and described the stabilizing effect of the moon on the climate of the earth. Foing who is also working as a scientist for space exploration projects of the ESA, invited medical scientists who are interested in this kind of work to bring in their specific expertise – water supply would be one of the most important challenges of the colonization of other planets.

Joint ERA-EDTA/Lancet Symposium

Collaboration reflects the growing influence of European nephrology.

In the run-up to this year’s annual meeting the ERA-EDTA and The Lancet medical journals have started a successful collaboration, which resulted in no fewer than seven contributions in The Lancet, one of the most prestigious medical journals in the world.

“...The Lancet journals were interested in working with us is a clear indication of the growing importance of European nephrology within the scientific community. For the ERA-EDTA, this media partnership is a supreme accolade”, commented Professor Raymond Vanholder, President of the ERA-EDTA. Yesterday, some of these Lancet publications were subject of a joint ERA-EDTA/The Lancet symposium at the Congress. Topics included the efficacy of a new efalizumab agent in diabetics with chronic kidney disease (Uli Broeckl, Germany), sodium restriction and hydrochlorothiazide in diabetic nephropathy (Arjan J. Kwackerman, The Netherlands), rituximab for treating childhood-onset of steroid-dependent nephrotic syndrome, and new insights into the management of acute kidney injury (AKI).

Contrast-induced AKI is subject of a heated debate in nephrology. While there is consensus that adequate hydration is the simplest and most effective way of protecting renal function, the opinions about the optimal hydration protocol differ. New data presented by Somjit Brar from Los Angeles, USA, suggest that intravenous administration of normal saline, guided by the left ventricular end-diastolic pressure, is well tolerated and could substantially reduce the incidence of contrast-induced AKI and major adverse clinical events in patients undergoing cardiac catheterization. Further studies are needed, to test the proposed hydration regimen in high-risk patients.

For AKI in neonates, peritoneal dialysis is the therapy of choice; in some cases, however, it may not be feasible. According to new data presented by Claudio Ronco, Italy, CARPEDIEM is the first CRRT platform designed and developed for small pediatric patients and could change clinical practice with respect to the management of neonates with acute kidney injury. Moreover, the ability to combine extracorporeal treatments, such as plasma exchange, blood exchange, and single-pass albumin dialysis, with CRRT extends the range of supportive treatments for critically ill infants.

The Lancet/The Lancet Diabetes and Endocrinology – Review

Room: Auditorium
Date: 02-06-2014
From 11:45 to 13:15
Daily rhythms of life

Ueli Schibler will hold the plenary lecture on the mammalian circadian timing system

The mammalian circadian timing system: the daily rhythms of genes, cells, and organs" are the subject of the plenary lecture, that will be held by Ueli Schibler at the last day of this years’ ERA-EDTA Congress.

"Most physiological processes are subject to daily oscillations"

"In mammals, most physiological processes are subject to daily oscillations that are driven by an endogenous circadian timing system", the Ueli Schibler research group describes their project at the University of Geneva: “This system is composed of a master pacemaker in the brain’s suprachiasmatic nucleus (SCN) and subsidiary oscillators in virtually all body cells. Our research group uses state-of-the-art molecular technologies to dissect the circadian clockwork circuitry and the signal transduction pathways by which the SCN synchronizes cellular clocks in peripheral organs.”

Schibler studied biology at the University of Bern and obtained his Ph.D. in 1975. During his thesis project, he compared the secondary structure of pre-ribosomal and ribosomal RNA during vertebrate evolution. From 1975 to 1978 Schibler worked as a postdoctoral fellow on mRNA 5’-capping and immunoglobulin mRNA processing in Robert Perry’s laboratory at the Fox Chase Cancer Center in Philadelphia. He then joined the Swiss Institute for Experimental Cancer Research (ISREC), first as a junior group leader (1978 to 1981) and then as a senior group leader with tenure (1981 to 1984). In 1984, Schibler joined the Department of Molecular Biology at the University of Geneva as a full professor.

Numerous Awards

Schibler is a member of several scientific associations, including EMBO, the European Academy of Sciences, the Swiss Academy of Medical Sciences, Faculty of 1000, and Union of Swiss Societies in Experimental Biology. He received numerous awards, amongst them the Friedrich Miescher Award of the Swiss Biochemical Society in 1983, the Cloetta Prize for Medicine in 1986, the Otto Naegeli Prize for Medicine in 1996, the Louis Jeantet Prize for Medicine in 2000 and the Aschoff and Homma Price in 2012.

More information on the research of the Schibler group: www.molbio.unige.ch/eng/research_groups/schibler/objectifs

Plenary Lecture 3: The Mammalian Circadian Timing System: the daily rhythms of genes, cells, and organs

Room: HALL 2
Date: 03-06-2014
From 9.45 to 10.30

Fighting inequalities

EKHA Spring Forum adresses the EU Parliament to ensure access to kidney health care

Lots of work is to be done to provide universal access to high quality kidney care in all European countries. Still, access to renal replacement therapy across borders and the efforts of different countries to contain costs differ mainly because of differences in health care systems.

To stop these inequalities and to promote kidney health are the most important aims of European Kidney Health Alliance (EKHA), which has made a big step forward in its activities with the organization of the EKHA Spring Forum at the EU Parliament in Brussels. Together with the MEP (Member of Parliament) Group for Kidney Health – led by MEP Mrs Zofija Macej-Kukovic (Slovenia) – EKHA brought all key European and national stakeholders together, including patients, nurses, foundations, experts and policy makers to discuss the issues surrounding the provision of kidney care in Europe.

"We all have to face these challenges and fight the inequalities", Prof. Norbert Lameire, EKHA Chair and host of the meeting pointed out. While recognising that the European Institutions support advances in kidney care through funding for research and joint actions on prevention of chronic diseases in general, experts agree that there is an urgent need for more integrated action underpinned by evidence. Sharing of best practice guidelines for CKD, examination of barriers to care choice at the national level, and improved awareness of these issues, are first steps towards improved standards of kidney care for Europeans.
Promoting peritoneal dialysis

EuroPD - an ERA-EDTA endorsed working group - fights underprescription in Europe

Peritoneal dialysis (PD) is an important form of treatment for patients with end-stage kidney failure requiring renal replacement therapy, yet the percentage of patients treated with PD is still low in Europe, ranging from 4% in Austria, Norway and parts of Spain to 11% in Denmark and Romania but higher in the UK. From the medical perspective, the outcomes of haemodialysis and PD are equivalent, and some specific patient groups, e.g. the young, may even gain by starting their renal replacement therapy on PD. PD also has the major advantage of being a home dialysis therapy. This means that, instead of having to go to a dialysis centre for haemodialysis three times a week for about four hours, PD patients can have much greater flexibility. They can choose when and where to dialyse – and this may enable them to keep their job or to go on vacation. The treatment can also better be adapted to the lifestyle of the patient, and patients are empowered to be "on the driving seat" of their own treatment and life.

PD remains underprescribed, and many patients are not even offered this modality, as was apparent from a recent large European patient survey. In December 2013 an ERA-EDTA and Euro-PD established a collaborative partnership with the aim of promoting PD in Europe.

In Amsterdam two symposia, a CME-course and a "free communication"-session are dedicated to PD so the attendees of the 51st ERA-EDTA Congress may gain insights into this treatment, its advantages and possible complications and up to date developments.

"The goal of Euro PD is to promote, support and expand knowledge, research and clinical practice in peritoneal dialysis", comments Prof. Nicholas Topley, Cardiff, UK, President of EuroPD. "Working more closely with ERA-EDTA will allow us to reach a wider audience, and keep the utility and excellence of peritoneal dialysis more readily in the focus point of nephrologists. EuroPD was founded in 1993, and supports research and education in the field of PD through its biennial conference and CME sessions at International meetings."

"PD is a key method of renal replacement and could be used to treat at least 15 to 20% of dialysis patients. PD has a positive impact on quality of life, because it promotes self-management and empowers patients with more choice, information and control. ERA-EDTA is eager to promote PD in Europe and has therefore agreed to establish this collaboration with EuroPD with as one of the main purposes to promote PD education", explains ERA-EDTA president, Prof. Raymond Vanholder, Ghent, Belgium. "We have to focus moving forward on improving the knowledge and training of nephrologists in the field of peritoneal dialysis."

Prevention of renal and vascular disease

Since 2010 an endorsed Working Group of the ERA-EDTA: European Uremic Toxin (EUTOX)

The European Uremic Toxin (EUTox) Work Group, since 2010 an endorsed Working Group of the ERA-EDTA, is committed to the prevention of vascular and kidney disease now in order to save lives and costs in the future. EUTox was launched by Raymond Vanholder, Bernd G. Stegmayr and Ulrich Baumeister in 1999 as a working group of the European Society of Artificial Organs (ESAO). In September 2000, at the occasion of the 27th ESAO-meeting in Lausanne, the Work Group convened for its first meeting.

Increasing costs

Currently, the costs of vascular and kidney diseases "are in the range of 500 billion Euros per year, increasing at a rate of ca. 10% per year", EUTox informs in its mission statement.

The mission statement continues: "Recent reports including our own data clearly indicate that a large proportion of renal, cardiovascular and/or cerebrovascular diseases are based on a common background, namely vascular lesions including endothelial cell damage. In fact, this may be detectable in the kidney initially since the kidney has the highest proportion of microvasculature. In later stages of the disease, damage to larger vessels and organs will become evident. Disease progression is enhanced by age, since lesions accumulate during life time and a reduced ability of repair. It is also enhanced by conditions like diabetes mellitus and the metabolic syndrome. As a consequence many renal, cardiovascular, and cerebrovascular diseases can be considered as systemic disorders affecting the (micro)vasculature.

It is currently impossible to cure these diseases at advanced stages. However, treatment can reduce or even stop disease progression. Unfortunately, as mentioned above, a state-of-the-art treatment with the aim to slow disease progression will not be available for all affected patients of the European population without a financial collapse of the public health system. The later treatments begin, the higher will be the resulting costs. In addition, quality of life is gradually reduced in advanced stages of disease. As a consequence, it is imperative to find ways to detect and treat this disease complex in early stages to ensure a higher quality of life for elderly Europeans and to save costs."

The aim of the group is to "prevent renal and vascular disease by: defining biomarkers that would allow early diagnosis of disease onset, identifying compounds that delay or halt disease progression, improving therapeutic strategies aimed at prevention of disease and disease progression."

EUTox will develop potential strategies to cope with these challenges and apply these almost immediately in the clinical setting."

Renowned clinicians from large clinical centres, leading clinical and basic scientists, highly innovative biotech companies and major medical and pharmaceutical companies are cooperation in the working group. It supports the scientific work of young nephrologists: In the past years 14 PhD students completed their thesis within the EUTox working group.

Uremic toxin database

Another important initiative is the uremic toxin database, a web-based, interactive tool both providing and collecting information on biological significance of uremic solutes.

Periodically EUTox offers CME courses for interested nephrologists. After a meeting in Madrid in March 2014 at the first day of the 51st ERA-EDTA Congress in Amsterdam EUTox followed by another highly interesting CME programme in October in Montpellier (France).
New Artis Physio™ system
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Visit us at booth E4

References
Metabolomics and uremia

Novel techniques for the detection of unknown markers

Metabolomics is one of the novel “omics” techniques that emerged in the last decade, allowing the detection of unknown markers for diseases in an unbiased manner, without targeted approach. This became possible only since strong analytical techniques for the assessment of large numbers of compounds became available together with biostatistical approaches allowing the dissection of complex conditions.

Among “omics” strategies, metabolomics is positioned most downstream of the biological action chain, and metabolomics is one of the novel approaches that emerged the last decade, allowing the detection of unknown markers; the problem is that this approach does not allow to specify their pathophysiologic importance. For this to come to pass, all newly recognized solutes in a second step need to be assessed by a targeted approach for their concentration, and then for their potential pathophysiologic effects. This should be preceded by an assessment of the metabolic potential of identified compounds.

The same approach can also be used for more specific studies, e.g. the detection of volatile gaseous solutes by analysis of breath, or the identification of compounds generated by the colon, by comparing dialysis patients with colon to some without a colon. Metabolomics has also been used to compare excretion of metabolites specific to certain diseases (e.g. Focal Segmental Glomerulosclerosis compared to other causes of nephrotic syndrome) or to compare dialysis strategies (e.g. low-flux vs. high-flux hemodialysis). Perhaps the most promising area in CKD for which metabolomics has been applied up to now, is the identification of metabolites potentially related to progression of renal disease. In this respect, many different approaches have been used. One of those is the search for metabolites serving as substrates for specific pump systems (e.g. Organic Anion Transporters – OATs) that have been linked to progression of renal failure by induction of tubular damage. In the same line, also metabolites in glomerular disease linked to morphologic tubulo-interstitial damage, another factor associated to CKD progression, have been assessed. Also solutes specifically adsorbed by the sorbent AST-120 (KremezinR), which has been associated with prevention of progression, have been identified by metabolomics. Similarly, also markers linked to prevention of progression by other approaches (e.g. Angiotensin Converting Enzyme inhibition – ACEi) have been studied.

When summarizing the several compounds that by metabolomic approaches have been associated to progression or its prevention, the predominance of organic acids is striking. The most predominant compounds unrazed by this approach are the hippurates (especially hippuric acid), followed by indoles (indoxyl sulfate), phenols (p-cresyl sulfate) and purines (uric acid, and – in animals – allantoin). Therefore, it seems worthwhile to further study the association of these compounds to progression of renal disease.

Stromal cell therapy for kidney repair?

Looking for alternatives to renal replacement therapy

The ageing population and the increasing prevalence of noncommunicable diseases such as diabetes and hypertension have led to an increased prevalence of chronic kidney disease. The generation of de novo kidney tissue from embryonic tissue and stem cells using tissue engineering approaches is being explored as an alternative to renal replacement therapy for treating the disease.

It is, however, becoming clear that resident cells cannot only induce fibrotic repair, but can also restore damaged kidney tissue. Mobilising this innate capacity of the kidney to regenerate is of particular interest in the prevention of irreversible kidney failure. A novel concept is that the interaction of interstitial stromal cells with the local immune system may regulate tissue homeostasis and the balance between tissue repair and fibrosis. Mesenchymal stromal cells (MSCs), in particular, may enhance the intrinsic reparative capability of the (transplanted) kidney. As mesenchymal stromal cells (MSCs) have potent anti-inflammatory and anti-fibrotic properties, these cells are of particular interest as new candidates in clinical treatment of transplant recipients. MSCs might play roles in the treatment of allograft rejection and fibrosis and in calcineurin minimization and induction protocols. The talk at the EDTA/ERA will consider the innate regenerative potential of stromal cells that are derived of the kidney as well as the current state of the art with respect to the use of bone marrow derived MSCs in kidney disease.

There is a need for alternatives to renal replacement therapy due to the increased prevalence of chronic kidney disease.
Reducing the cardiovascular risk of uremia

Volatile uremic toxins and related gaseous compounds

The field of uremic toxicity covers the study of a large number of different substances, classified in relation to their characteristics, for example protein-binding, dimensions, etc. The endogenous compounds of gaseous nature have lately received much consideration, because of their increasingly recognized importance in health and disease. Among these substances, some are uremic toxins per se, others are related to uremic toxins, or can become toxic under some circumstances. We can divide them into two broad categories: organic and inorganic compounds.

Among the organic compounds, Volatile Organic Compounds (VOCs) in human blood may be of endogenous or exogenous origin. Some of the volatile compounds in the blood are excreted via the kidneys. Therefore, they may accumulate in renal failure. Phenols, indols, 2-methoxyresorcinol, p-hydroxy hippuric acid, and phenyl acetic acid, trimethylamine and dimethylamine are listed among these substances. These substances are characterized by their strong pathophysiological effect and an adequate vapor pressure sufficient for extrapulmonary elimination.

Among the inorganic solutes, ammonia is present. Renal failure results in accumulation of urea in the body fluids leading to massive diffusion of urea in the gastrointestinal (GI) tract. The rise in urea concentration in the GI tract leads to the preponderance of urease-possessing bacteria. Hydrolysis of urea by microbial urease leads to the formation of massive amounts of ammonia and ammonium hydroxide, which are able to interact between themselves and influence their respective action in a complex manner.

All these gases have in common that, in the past, they were considered to be just toxic compounds and environmental pollutants, and only recently their biological functions have been appreciated. In addition, small size, brief half-life, and the capacity to easily cross membranes, are shared features.

H$_2$S is a poisonous gas with a typical odor of rotten eggs. H$_2$S is liberated in toxic amounts by decaying organic matter, or, in refineries and oil gas fields, it represents a major safety hazard. However, the first life forms tolerated and even produced H$_2$S, as a metabolic fuel (Figure 1). H$_2$S thus represents the third endogenous gaso-transmitter, along with NO and CO.

Three enzymes catalyze the formation of H$_2$S: cystathionine beta-synthase (CBS), cystathioninylase (CSE), and 3-mercaptopropionate sulfoxtransferase (MST). In the liver, kidney, enterocytes, vascular smooth muscle cells, and endothelial cells, H$_2$S is formed by CBS, while in the brain its production is mainly attributed to CBS. In addition, MST is operative at cardiac, kidney, and brain levels, and in the vascular endothelium.

H$_2$S is involved in general as a protective agent in oxidation, inflammation, apoptosis, all events paving the way to acute and chronic diseases such as ischemia-reperfusion injury, pulmonary hypertension, atherosclerosis, chronic kidney disease (CKD) progression and complications.

Evidence shows that H$_2$S is involved in aging by inhibiting free-radical reactions, activating SIRT1, and probably interacting with the age-related gene Klotho. H$_2$S concentration is decreased in the plasma of hemodialysis patients. Red cell sulffhemoglobin (a putative marker of chronic H$_2$S exposure) levels, is low in this patient population, and is accompanied by high plasma homocysteine and cysteine, with a significant negative correlation between cysteine and H$_2$S Gene expression of CSE in blood mononuclear cells is significantly lower, realizing a condition where a transcriptional downregulation of the gene encoding for a key H$_2$S-producing enzyme is present.

These findings are in accordance with the existence of one or more uremic toxins inhibiting both CBS and CSE, without excluding the presence of post-translational modifications.

After a single dialysis session, plasma H$_2$S levels increase significantly, a finding which is compatible both with the idea that dialysis eliminates a uremic toxin which inhibits the H$_2$S-generating enzymes, and with the idea that dialysis hypotension could be due to H$_2$S release. The interactions between NO, CO, and H$_2$S have been proven by many studies. For example, H$_2$S exerts a double-faced interaction upon NO. H$_2$S could, through the formation of a putative nitrosothiol, bind to NO and therefore decrease its availability or independently from the formation of this adduct. Other authors have shown that H$_2$S enhances the vasorelaxant effects of NO. NO donor drugs enhance H$_2$S production and increase CBS expression in smooth muscle cells. There are many ways through which H$_2$S interacts with NO, aside from nitrosation formation. Recent work shows a cooperative interaction between H$_2$S and NO, which increases and maintains cellular cGMP levels essential for vasorelaxation and angiogenesis and reveals the potential for each of these molecules to control the actions and effective concentration of the other.

The therapeutic potential related to these gases is still in its infancy, with the exception of NO in treatment of lung disease of the newborn. First of all, the exact pathologies where these gases should be employed are not clear; the form of the gas donor is being investigated as well, and many other questions are still open. However, this field shows much promise. For example, strategies aimed at lowering the urea and VOCs burden by moderate reduction in protein intake and longer and more frequent dialysis may attenuate CKD-associated systemic inflammation and improve CKD/ESRD patients’ well-being and survival. Use of oral adsorbents such as AST-120 to remove ammonia may prove beneficial.

Use of NO-, CO-, and H$_2$S-donors is under active scrutiny for ameliorating the ischemia-reperfusion injury present in transplantation and other situations, and for reducing the cardiovascular risk of uremia.

Alessandra F. Perna, Naples, Italy

S 36: The novel uremic toxins: what did we learn recently?
Room: HALL 2
Date: 03-06-2014
From 8:00 to 9:30

Reference

New hope for therapeutic applications

Generation of functional kidney tissue from cell suspensions

Over 1.8 million people worldwide with end-stage renal disease are alive only because they have access to dialysis or kidney transplantation. The alarming rise of this figure in the developed world – estimated at 6 to 11 per cent annually – together with the insufficiency of suitable renal allografts to meet growing demand, creates an imperative need for tissue-engineered alternatives.

Engineering a whole kidney is still unfeasible, and indeed a daunting task. It requires an intact 3D-scaffold from bio-printing or de-cellularisation approaches, with accurately positioned basement membranes of each nephron, a corresponding number of vessels, collecting ducts, and finally to repopulate each element with the correct cell type. An alternative approach that could minimise the requirement for engineering is to exploit the self-organising abilities of the cells to generate a ‘fetal’ form of the organ, which can then be provided with the appropriate developmental niche to grow and mature.

One of the earliest descriptions of this concept demonstrated that suspensions of metanephric mesenchyme cells can be induced by spinal cord cells to generate in vitro a 3D renal tissue, which contains rudimentary nephron-like structures (1). Important progress on the field has recently been made by the development of a method that allows a simple suspension of embryonic kidney cells to self-organise in vitro into a ‘tissue’ containing immature nephrons and collecting ducts, without the use of any exogenous tissue (2). These attempts, however, did not show development of glomeruli in any meaningful extent. The avascular in vitro environment, does not allow formation of glomeruli – the key step towards building a functional kidney tissue.

A new protocol of organoid construction

Dealing with this challenge, we attempted to generate functional renal tissue from suspensions of murine E11.5 kidney cells. In the first set of experiments, we employed a new protocol of organoid construction, starting from a large cell aggregate culture that appeared to be of utmost methodological importance to achieve the formation of viable nephrons in vivo. Although the newly formed kidney tissue survived transplantation, podocyte structure and function represents a critical prerequisite for any kidney-engineering attempt to establish efficient filtration. In this respect, we provided evidence for slit diaphragm formation in the engineered organoids. It was not yet clear, however, whether the degree of maturation of newly created podocytes was high enough to serve sieving function that selectively restricts the passage of circulating high molecular weight macromolecules across the glomerular barrier.

Analysis of the implanted organoids

To answer this question we employed a highly sensitive in-lens Scanning Electron Microscopy detection system that allows analysis of the deepest region of the glomerular filtration slits, in combination with macromolecular tracing experiments. Analysis of implanted organoids showed irregular filtration pores, which were heterogeneous, both in size and shape within the podocyte junctions. The epithelial pores were mainly located in the central region of the filtration slits and their dimensions resembled those of adult healthy murine kidney. To test whether the nephrons of the engineered tissue could exert physiological permissive function, we injected FITC-, RITC- or TRITC-conjugated dextrans (10, 70 or 155 kDa, respectively) into host blood system and analysed their localization by fluorescence microscopy. All the dextrans were found in α-actinin 4-positive glomeruli, but only those of lower molecular weight were concentrated at the apical pole of proximal tubular cells. Together these data demonstrate that newly formed glomeruli developed the adult structural framework of the slit diaphragm that could support filtering function and restriction of macromolecular trafficking toward the tubular lumen.

The capacity to build functional kidney tissue starting from suspensions of individual cells provides a solid methodological basis for a number of investigative applications. Based on our data, one may anticipate self-organising organoids can be successfully applied to provide a ‘bio-scaffold’ in the construction of transplantable kidney tissue starting from human stem cells.
Indeed, organoids have been shown to incorporate cells of another source, such as induced pluripotent stem cell-derived kidney progenitors (4) to build a chimeric tissue in vitro. Recent data from our lab showed that human amniotic fluid stem cells, an embryonic-like cell type, are efficiently patterned by the spatial information of mouse self-forming organoids to form 3D chimeric tissues. These chimeras survived for several days in vitro, and further grew when implanted into a living recipient, to generate 3D nephrons endowed with tubuli. Growing and transplanting chimeras that combine animal progenitor cells and human stem cells, followed by the selective elimination of animal cells after transplantation, may constitute a plausible way to generate and deliver donor tissue. By permitting the aggregation of stem cells derived from individual patients in the chimeras, this protocol can also be applied to test effects of patient’s mutations or disease-related genes on cell fate in 3D functional kidney tissue.

Overall, this system, previously unfeasible in mammalian kidney, will be of great immediate interest for developmental and disease-modeling studies, and provide hopes for cell-based therapeutic applications.

References

Prognostic marker or an active player?
The role of endocan in inflammation and mortality in CKD

During the past 20 years, proteoglycans have emerged as critical modulators of most major cellular processes, including cell proliferation, adhesion, and migration. Endocan, previously called endothelial cell specific molecule-1, is a soluble proteoglycan of 50 KDa expressed by the vascular endothelium. Endocan is the product of one single gene, esm, located in the proximal region of chromosome 5 long arm (5q11.2).

Overexpressed in cancer, sepsis obesity and inflammation

Increasing experimental evidence has reported that Endocan is overexpressed in cancer, sepsis, obesity, or inflammatory conditions and that it is related to patients’ outcome in some of these conditions, including sepsis and cancer. Endocan may play a role in the vascular contribution to organ-specific inflammation and in endothelium-dependent pathological disorders; most importantly it may represent a novel endothelial cell dysfunction marker.

Endothelial dysfunction is widely regarded as being involved in the development of atherosclerosis. In addition, vascular inflammation is an important process in the pathogenesis of cardiovascular disease (CVD). An initial step in vascular inflammation leading to atherosclerosis is the adhesion cascade, which involves the rolling, tethering, adherence and subsequent transmigration of leukocytes through the endothelium. Recruitment and accumulation of leukocytes to the endothelium is mediated by an upregulation of adhesion molecules such as vascular cell adhesion molecule-1 and intracellular adhesion molecule-1 (ICAM-1). Endocan affects the interaction ICAM-1/LFA-1, and may be implicated in the regulation of leukocyte extravasation at the inflammation sites.

In patients with psoriasis or newly diagnosed hypertension, endocan levels were strongly correlated with both hsCRP and CIMT values. Recently, it was also shown that in patients with Behçet disease (a systemic immunoinflammatory vasculitis characterised by endothelial dysfunction), Endocan levels were associated with hsCRP.

Endothelial cells also play a key role in sepsis, by producing cytokines and chemotactic factors and expressing surface adhesion molecules that induce circulating leukocytes migration into tissues. The increase of circulating endocan in sepsis may not only reflect the intensity of endothelial activation and injury but also participate in the natural anti-inflammatory response of the body. A high level of circulating endocan during the early stages of sepsis was associated with a lower probability of survival 10 and 28 days later. Endocan had a higher discriminant value for predicting septic shock and death than the von Willebrand factor and thus could represent a useful marker for severity and outcome of sepsis.

CKD patients are well-known for the extreme high risk of CVD. Reduced kidney function is associated, among other, with increased levels of inflammatory factors and endothelial dysfunction. Identifying biomarkers that would serve as indicators of widespread inflammation or as surrogates for endothelial cell activation and/or dysfunction is of particular importance. Endocan expression is mediated through a VEGF dependent signaling pathway. Microenvironments that are rich in VEGF, like CKD, may activate both PKC-NF-κB and PI3K-AKT forking pathways in the endothelium, resulting in a net induction of Endocan gene expression.

Endothelial cells first recognised by the immune system

Endothelial cells are sites of early contact between donor and recipient cells, and are first recognised by the immune system after organ transplantation. The persistent injury results in excessive turnover of graft vascular endothelial cells in renal allografts, so long-term renal transplant inflammation and endothelial activation may play a relevant role in inflammation, organ fibrosis, and graft dysfunction. In a recent cross-sectional study of 97 renal transplant recipients, Su et al. observed a correlation between serum Endocan level and CKD stage of a graft kidney, and also that a high level of circulating Endocan was associated with progression of graft renal function at 3 months. Interestingly, they also found a statistically significant correlation between Endocan and TNF-α, a cytokine that is known to stimulate endothelial cell activation and injury. In healthy subjects, TNF-α is usually not present in the kidneys, but is stimulated by and detected in rejected allografts, diabetic nephropathy, and glomerulonephritis.

We evaluated plasma Endocan levels in 61 CKD (stage 1 to 5) and 60 control patients. All-cause mortality and cardiovascular events (CVE) were also analysed in relation with plasma Endocan levels. Patients with CKD showed increased Endocan levels, with values progressively higher across the CKD stages. In a multiple linear regression model, including predictors of Endocan, FMD, CIMT, hs-CRP, maintained an independent association with Endocan. In multivariable Cox models, after adjustment for traditional and renal specific risk factors Endocan levels maintained an independent association with outcomes (follow-up period of 42 months).

Further studies are needed to determine if Endocan is only a marker of a negative prognosis in this patients or an active player in the CKD-inflammation-endothelial dysfunction interconnection.

Adrián Covic, Iasi, Romania

S 41: Inflammation and cardiovascu-
lar toxicity in chronic kidney disease

Room: AUDITORIUM
Date: 03–06–2014
From 10:45 to 12:15
A health risk in and beyond CKD?

Dietary phosphate intake

In patients with chronic kidney disease (CKD), especially in advanced stages, phosphate is retained in the organism since the failing kidneys are less and less capable of excreting the phosphate ingested with the meals and absorbed from the intestinal lumen. Therefore, the overall phosphate balance tends to become positive, and phosphate together with calcium is to be found in association with soft tissues including vascular tissues since such excessive amounts of phosphate cannot be taken up by the bones. The observation that high extracellular phosphate levels, in presence of normal or high extracellular calcium levels, favor vascular calcification is based on numerous clinical observations and experimental in vitro and in vivo findings.

Interaction with a complex regulatory system

It must be noted, however, that in the in vivo setting phosphate does not act in an isolated fashion but in interaction with a complex regulatory system including parathyroid hormone (PTH), 1,25 dihydroxy vitamin D (calcitriol), fibroblast growth factor-23 (FGF23) and Klotho. Only in vitro experiments allow one to separate direct phosphate effects from those mediated by other factors whose circulating and local concentrations are influenced by this ion and which control phosphate homeostasis.

Most importantly, in recent years hyperphosphataemia has been found to be associated with an increase in the relative risk of cardiovascular morbidity, cardiovascular mortality and all-cause mortality in patients with CKD. Block et al (JASN 2004) who studied a cohort of 40.538 patients on hemodialysis therapy found, after adjustment for confounding factors, that 12 % of the 10.015 deaths occurring over the observation period were linked to increased serum phosphate levels.

Again, whether this association is due to a direct phosphate action on the myocardium, as suggested by association studies, or due to indirect effects via PTH, calcitriol, FGF23 and Klotho, or all these factors combined remains to be seen.

An association – no proof of a causal relationship

The finding of an association is no proof of a causal relationship. It is only hypothesis generating. Unfortunately, so far no randomised controlled trials (RCT) have ever tested the hypothesis that lowering high serum phosphate levels to less high or normal values reduced high patient outcomes and improved survival. To the best of our knowledge, even for surrogate parameters such as vascular calcification there is only one RCT, by Russo et al (Kidney Int 2007) which has assessed the effect of dietary phosphate restriction on vascular calcification, in this case coronary artery calcification. However, the study was not designed to show a superiority or an equivalence of dietary phosphate modification, as compared to oral phosphate binders.

The Italian investigators recruited 90 phosphate-binder-naive patients with CKD stages 3–5 who were not on dialysis. Of these patients, 30 were randomised to a low-phosphate diet alone, with the remaining 60 patients receiving the same diet in combination with fixed doses of calcium carbonate or sevelamer-HCl over a 2-year follow-up period. Final coronary artery calcification scores were increased in the group receiving phosphate-restricted diet alone and in the group receiving diet in combination with calcium carbonate. In contrast, there was no progression of calcification in the diet-plus-sevelamer-treated group. It is noteworthy that the prescription of phosphate restriction alone did not lead to a decrease in urinary phosphate excretion. Thus, a low phosphate diet alone did not prevent CKD-associated progression of coronary artery calcification in patients not receiving dialysis.

Several therapeutic strategies can be used to avoid excessive phosphate accumulation. Approaches include reducing phosphate intake by dietary modifications, reducing intestinal absorption using phosphate-binding agents, and in patients with severe CKD who require renal replacement therapy (CKD stage 5D), increasing removal of phosphate with more efficient dialysis.

Dietary phosphate restriction has long been recommended in patients with CKD, together with dietary protein restriction to slow the progression of CKD since diets rich in protein are usually also rich in phosphate. Although this approach has been proven to be beneficial in slowing the progression of vascular calcification in several experimental studies in animals with CKD convincing proof for a similar benefit in human patients with progressive CKD is still lacking. Moreover, severe restriction of protein and phosphate intake may lead to malnutrition, with potentially serious negative consequences for patient well-being and outcome.

Phosphate content of different protein sources

Recently it has been shown that the phosphate content of different protein sources differs. Protein sources of phosphate may be mainly meat/casein (typical Western diet) or vegetarian/origin. The grain-based diet has a lower phosphate-to-protein ratio and much of the phosphate is in the form of phytate, which is not absorbed by most mammals. Grain-based vegetarian diets lead to decreased phosphate absorption compared with meat- or casein-based diets. The source of protein has a significant effect on phosphate homeostasis in patients with CKD.

Dietary counseling of patients with CKD should include information on not only the amount of phosphate but also the source of protein from which the phosphate derives.

Use as a food additive and preservative

Another phosphate source that has not attracted sufficient attention to date arises from the increased use of phosphate as a food additive and preservative. This ‘free’, not organically bound phosphate is effectively absorbed from the gastrointestinal lumen. Typical foods with large amounts of added phosphate are processed meat, ham, sausages, canned fish, baked goods, cola drinks, and other soft drinks.

Dietary counseling is all the more difficult because the phosphate content in food – and, in particular, the added phosphate content – is not marked on the package.

Conclusion

Hyperphosphataemia has been repeatedly found to be associated with cardiovascular dysfunction, vascular and valvular calcification and increased mortality. However, there is insufficient evidence at present to strongly endorse dietary phosphate restriction as the primary intervention for the management of hyper-
phosphate removal. Limited safety data suggest that dietary phosphate restriction does not compromise nutrition in a monitored setting. A reasonable approach appears to be a moderate dietary phosphate and protein restriction, together with avoidance of phosphate enriched food and beverages.

What is Wnt signalling?

**Sclerostin and DKK-1: potential role in CKD-MBD**

Wnt signalling pathways play a key role in a large variety of diverse biological processes such as cell proliferation, growth, migration, and differentiation. Wnt signalling encompasses at least three different complex pathways one of which is the “canonical” Wnt/beta-catenin pathway. The canonical Wnt pathway involves interaction of several Wnt ligands and inhibitors with a transmembrane receptor complex (Frizzled) including the co-receptors low-density lipoprotein-related proteins 5 and 6 (LRP5/6). With activation of this receptor complex, cytoplasmic beta-catenin degradation via phosphorylation is diminished. In consequence, beta-catenin accumulates intracellularly and allows more beta-catenin to translocate into the nucleus where beta-catenin assists in the activation of various target genes. Wnt signalling including soluble inhibitors is extensively described in bone physiology and regulation of bone cellular activities as well as mineralization processes.

**Sclerostin and DKK-1 as Wnt inhibitors**

Wnt inhibitors are soluble extracellular secreted factors that interact e.g. with Wnt receptors or Wnt ligands and attenuate Wnt signalling activity. Both sclerostin and DKK-1 proteins are soluble Wnt-inhibitors. They both have undergone some experimental and clinical investigations in the field of CKD-MBD and are measurable in human blood via ELISA techniques. Despite some homologies in action it is important to note that DKK1 and sclerostin exhibit distinct biological effects and are differently regulated. Based on previous experimental findings specifications emerged that sclerostin might exert more selected regulatory actions while DKK1 might more be a pan-Wnt inhibitory blocking protein, since its actions include various Wnt classes. Accordingly, dramatic differences exist between the two rodent knock-out models SOST-/- and DKK1-/-.

SOST-deficiency results in a relatively benign phenotype with predominant skeletal changes. In contrast, DKK1-/- animals die prematurely from severe developmental defects. Sclerostin is secreted almost exclusively from bone by osteocytes and to a lesser extent by other cell types including e.g. osteoclast precursors.

Both Wnt inhibitors interact with the LRP 5/6 and therefore accelerate catenin degradation and finally prevent catenin transcriptional activities in the nucleus. However, the binding to LRP 5/6 involves different co-receptors for sclerostin and DKK1 – another proof that clearly points towards different physiological functions. The role of Wnt signalling and its inhibition regarding skeletal health can easily be elucidated in human and rodent genetic modification models including sclerostosis and Van Buchem’s disease. While reduced activity of sclerostin and DKK1 contribute to increased bone mass and strength the opposite is true in experimental models with overexpression of both sclerostin and DKK1. The latter condition is characterised by skeletal defects and/or osteopenia and osteoporosis.

**Wnt signalling in CKD-MBD**

In vivo data show that osteocytic dysfunction, augmented sclerostin expression and reduced osteocytic Wnt/beta-catenin signalling are early findings during the development of CKD-MBD. Elevated circulating sclerostin levels are detectable in humans with advanced or end-stage renal disease compared to individuals with normal renal function, which does not translate into reduced general Wnt/beta-catenin activity in CKD as indicated by increased genetic expression profiles in monocytes from CKD patients. When comparing blood sclerostin measurements in CKD patients significant discrepancies need to be taken into account with different sclerostin assays applied. It is currently incompletely understood if these increased levels in CKD reflect increased production, renal retention or both. A particularly relevant subtype of renal osteodystrophy is adynamic bone disease (ABD) characterised by substantially reduced bone formation rate, impaired remodelling activity and reduced cellular activities, and in part mediated by relative low levels of PTH or PTH resistance. In CKD-MBD potential interactions between PTH and Wnt signalling are of particular interest, however, incompletely understood. PTH effects upon bone are clearly dependent of sclerostin activity as shown in animal models with sclerostin overexpression and deficiency. Without physiological sclerostin action PTH cannot affect bone metabolism appropriately. Preliminary results from a cross-sectional bone biopsy study in 60 dialysis patients revealed a statistically negative correlation between serum sclerostin and PTH. Moreover, sclerostin showed strong negative associations with parameters of bone turnover pointing towards a role of high sclerostin levels in induction of ABD, or ABD disease inducing upregulation of the SOST gene. In contrast, no such association was found for DKK1. Of note, strong experimental evidence supports a crosstalk between PTH and Wnt signalling actions upon bone metabolism which is particularly true for sclerostin: While in vivo overexpression of DKK1 does not blunt the osteoanabolic effect of external PTH sclerostin overexpression in contrast reduced PTH-associated bone gain. It is currently speculative to what extent this PTH-sclerostin-crosstalk is preserved under uremic conditions and if high sclerostin levels contribute to uremic skeletal PTH-resistance.

**Wnt signalling in vascular disease**

Wnt signalling plays a crucial role in human atherosclerosis. Missense mutations in LRP6 for instance are associated with premature coronary artery disease. The role of Wnt inhibitors in uremic vascular disease is a novel, evolving field. Recent research indicated that in human calcified aortic valve tissue from hemodialysis patients a significant sclerostin mRNA upregulation is detectable compared to non-calcified controls. Experimental data confirm sclerostin expression in calcifying vascular smooth muscle cells (VSMC) in vitro. Occurrence of sclerostin in calcified tissue is also detectable in patients with calciphylaxis – a severe form of uremic small vessel calcification with consecutive ulcer development. However, we acknowledge that it remains to be demonstrated whether sclerostin in the vasculature exerts paracrine anti-mineralization effects similar as to in bone. Of note, several groups recently demonstrated that high circulating sclerostin levels are associated with improved survival in CKD / ESRD cohorts.

The puzzle is still incomplete and several important pieces are missing. Currently, Wnt signalling and its inhibitors are among the most fascinating evolving fields in CKD-MBD.
The role of local renal endothelium dysfunction

Renal endothelium in diabetic nephropathy

Diabetic nephropathy is the leading cause of end stage renal disease. Diabetes mellitus is characterized by generalized endothelial dysfunction. However, recent data also emphasize the role of local renal endothelium dysfunction in the pathogenesis of diabetic nephropathy.

Endothelial glyocalyx and glomular permselectivity

Diabetic nephropathy early in its course is characterised by microalbuminuria. Since the endothelium in glomerular capillaries is characterised by the presence of numerous transcellular fenestrations with a diameter ranging from 60 to 100 nm, it was thought that it does not play any role in the glomerular filtration barrier. A role was anticipated only for glomerular basement membrane and mainly for the slit diaphragm that spans between neighboring podocytes foot processes. However, recently the role of endothelium in glomerular permselectivity has been revised. By specific techniques it has been revealed that endothelial cells are covered by a 200 nm thick, rich in negatively charged proteoglycans and glycoproteins layer, covering both the fenestral and the interfenestral regions. This layer is called glyocalyx and its disruption leads to proteinuria in various experimental and in vivo studies.

Regarding diabetic nephropathy, in vitro studies in glomerular endothelial monolayers showed that hyperglycemia decreases the synthesis of heparan sulfate, a component of the glyocalyx, and increases the passage of albumin across the cell monolayer. Albuminuria in Zucker fatty rats was also evaluated in humans. In type I diabetic patients, glyocalyx volume decreased in a stepwise fashion from controls, diabetics without microalbuminuria and diabetics with microalbuminuria. Increased hyaluronidase contributed to these changes. Moreover, in type II diabetic patients, glyocalyx was found to be thinner and the transcapillary escape rate of albumin increased. Again increased hyaluronan catabolism contributed to these changes.

Fluctuations of VEGF expression

Another characteristic of diabetic nephropathy course is an early increase of glomerular filtration rate (GFR) followed by a progressive decrease. For the early increase of GFR, neoangiogenesis of the glomerular capillaries could be held responsible. Streptozotocin induced diabetes model demonstrated an increase in the glomerular capillary number, capillary length and capillary cross-sectional area. Similarly, neoangiogenesis was observed in human studies as well. Interestingly, neovessels are immature with thin basement membrane and endothelial swelling and possibly unable to preserve permselectivity, contributing to microalbuminuria.

However, the initial increase of GFR progressively declines in diabetic nephropathy. This could be the result of glomerular capillary rarefaction, which characterises advanced nephropathy. The initial increased and then gradually decreased glomerular capillaries could be attributed to similar alterations of the vascular endothelial growth factor-A (VEGF). VEGF plays a significant role in diabetic microangiopathy.

In the kidney VEGF is produced by the podocytes and its expression is increased in early diabetic nephropathy, promoting neoangiogenesis. In advanced diabetic nephropathy, possibly due to decreased podocytes, VEGF expression and activity decrease leading to glomerular capillary rarefaction and decreased GFR. In models of early diabetic nephropathy, anti-VEGF agents have beneficial effects. However, VEGF plays a significant role in vessel homeostasis and its inhibition could end up in renal damage as well.

Disturbances of NO availability

Nitric oxide production has a similar pattern with VEGF expression. Nitric oxide production is increased in early diabetes and its inhibition attenuates hyperfiltration. Urine nitrite and nitrate levels are increased in type 1 diabetic patients with microalbuminuria. However, decreased NO levels are correlated with advanced diabetic nephropathy as shown by a number of genetic polymorphisms that lead to decrease NO levels in humans. This was also confirmed by animal studies in endothelial nitric oxide synthase (eNOS) deficient mice. In humans and in animal models, eNOS expression in glomerular endothelium is increased. However, NO availability is decreased and oxidation of tetrahidroxiprotein, a cofactor of eNOS, by reactive nitrogen species has been incriminated. Interestingly, streptozotocin treated mice develop early pathological changes of diabetic nephropathy, whereas the same treatment in eNOS knock-out mice leads to pathological changes seen in advanced diabetic nephropathy, such as mesangiolysis, Kimmelstiel-Wilsod nodules, arterial hyalinosis and tubulointerstitial disease.

An underlying mechanism could be the disruption of glomerular autoregulation, which results in increased transmission of pressure to the glomerulus. Consistent with this, lowering blood pressure prevents glomerular injury in eNOS knock-out mice. Another possible mechanism could be the VEGF-eNOS uncoupling. Normally VEGF induces NO production, which exerts a protective role in glomerular endothelium. However, in case of reduced NO availability, VEGF induces uncontrolled excessive endothelial cell proliferation and macrophage infiltration. The role of NO in controlling VEGF action has also been detected in the retina of diabetic eNOS knock-out mice. Compared to wild diabetic mice, diabetic knock-out mice develop accelerated retinopathy, characterised by the formation of abnormal acellular retinal capillaries and increased retinal vascular permeability. Finally, NO inhibits exocytosis of Weibel-Palade bodies by endothelial cells. Thus in case of decreased NO availability, more von Willebrand factor and P-selectin are released making the endothelium prothrombotic.

Glomerular fenestral endothelium and GFR

Recent studies revealed that diabetic nephropathy is accompanied by reduced glomerular endothelial fenestration in patients with type 1 or type 2 diabetes. Interestingly, in the latter case the reduced endothelial fenestration was inversely related to GFR. It is likely that reduced endothelial fenestration lowers glomerular hydraulic permeability in diabetic nephropathy and decreases GFR.

A reduction in the density and size of endothelial fenestrae has been confirmed to play a key role in the decrease of GFR in women with preeclampsia, supporting the possibility of a similar pathogenetic mechanism in diabetic nephropathy. Interestingly, experimental studies showed that VEGF is required for the formation of glomerular endothelial fenestrae, and in patients with preeclampsia VEGF action is inhibited by the increased levels of its soluble receptor VEGF-R1. It remains to be elucidated if decreased VEGF expression in advanced diabetic nephropathy is responsible for reduced glomerular capillary fenestration, contributing to decreased GFR.

Endothelial progenitor cells

Although in higher vertebrates fibrosis is the predominant process of tissue repair, anagenesis also takes place albeit to a small extend. Endothelial progenitor cells (EPCs) are circulating...
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Led by a distinguished faculty of experts, this stimulating meeting has been designed to inform nephrologists of the potential for improved clinical outcomes and health-related quality of life with High Dose (short daily or nocturnal) Haemodialysis (HD) regimens, compared with conventional three-times-per-week HD. It will also demonstrate how barriers to Home HD may be overcome through innovations in HD device design, presenting a novel Home HD device for the first time.

Panel Discussion plus Q&A
Led by Pieter ter Wee

Summary and Closing Remarks
Pieter ter Wee
Coordinated studies

Immune mediated kidney diseases in children

The ERA-EDTA has established a task force with the European Society for Pediatric Nephrology (ESPN) on immune mediated renal diseases, launching combined activities between the Working Groups of the two Societies in order to establish coordinated studies on immunological renal diseases from childhood to adult and old ages.

Common renal biopsy survey

Diseases similar from a pathogenetic point of view, like nephrotic syndrome, IgA nephropathy, small vessel vasculitis as Henoch-Schoenlein purpura, ANCA vasculitides, present in different ages with slightly different symptoms, but, what is of great interest, with different natural history, various response to treatment and very different final outcomes. Most of the factors favouring the regression in children versus the progression in adults are unknown, hence it will be a fascinating experience to try to discover them.

The joint WGs activity has focused at first on a common renal biopsy survey, which was recently sent to members of the two societies in order to gather a broad overview of clinical indications and technical details for renal biopsy in children and in adults in native and transplanted kidneys. The questionnaire was prepared by Alessandro Amore as ESPN WG Coordinator in collaboration with the ESPN WG and the ERA-EDTA IWG, including L. Gesualdo, V. Tesar, J. Fiolege, D. Jayne and J. Egido. It was distributed as well to Pediatric Nephrology Centers by the ESPN, in order to get, if possible, a full view over all patients’ age. The expected results of a European survey and also from the non EU Mediterranean will provide information for preparing recommendations on the timing for performing renal biopsy in patients with proteinuria and/or hematuria or in cases of urinary abnormalities in different ages with slightly different symptoms, but, what is of great interest, with different natural history, various response to treatment and very different final outcomes.

The second initiative which represents great news in the field of immune mediated renal diseases in children is a collaboration of the ESPN WG of immune mediated renal disorders with the Columbia University, New York, USA on genome-wide association study (GWAS) in children with Henoch-Schoenlein Purpura (HSP) and primary IgA nephropathy (IgAN). IgAN represents the leading cause of kidney failure among young adults and the most frequent form of primary glomerulonephritis worldwide. Recent studies from A. Gharavi and K. Kyrlyuck defined IgAN as an autoimmune trait of complex architecture with a strong genetic determination. Several common genetic variants were found to predispose to IgAN in adults through a large-scale genome-wide association study (GWAS).

Higher burden of genetic risk factors

More recently, a strong relationship between the number of GWAS risk alleles and the age of disease onset was discovered, suggesting that pediatric patients with IgAN may carry a significantly higher burden of genetic risk factors. Accordingly, we are now extending our genetic investigations to children affected by IgAN and Henoch-Schoenlein purpura without or with nephritis.

Theodoros Eleftheriadis, University of Thessaly, Neo Ktirio, Mezourlo Hill, Greece

S59: Diabetic Nephropathy and Proteinuria
Room: ELICIUM 1
Date: 03-06-2014
From 8:00 to 9:30
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A growing interest in intensified dialysis
What is new - not only for children, but also for adults?

Over the past 20 years, children receiving dialysis have benefited not only from advances in modern technology, but also from improvements in clinical management. Until the 1980’s, hemodialysis (HD) was only prescribed as twice weekly dialysis sessions lasting 4 to 6 hours at one time. However, these sessions were often poorly tolerated, only offering survival, without quality of life. This led to changes in the dialysis regime over the 1990’s; twice weekly sessions were replaced by procedures performed three times a week. Nevertheless, despite decades of experience and technical improvements in performing three times a week in-center HD, children treated by this conventional dialysis regime still have an increased risk of cardiovascular morbidity, impaired growth, malnutrition due to protein wasting and bad volume control.

Growth retardation

As a result, there is a growing interest in the delivery of intensive hemodialysis. With conventional dialysis regime, there is often a loss in height standard deviation score (SDS) that can be correlated to the duration of dialysis, with a mean loss of 0.4 to 0.8 height SDS per dialysis year. This growth retardation, which occurs over the dialysis treatment period, is directly correlated with the final adult height, despite satisfactory kidney transplantation. Protein-energy malnutrition is an important cause of impaired growth. It comprises both malnutrition and cachexia. With conventional hemodialysis, children have to endure dietary restrictions, due to the intermittence of the dialysis sessions. They also need to take various medications on a daily basis, such as potassium or phosphate chelators, which contribute to anorexia. Indeed, if the dialysed child has good appetite, he is at risk of significant interdiytic weight gain and of elevated blood levels of phosphate or potassium, a situation that usually conducts to the enhancement of the duration of the dialysis session passing from 4 to 5 even 6 hours, even sometimes to the prescription of an additional dialysis session later in the week due to the unadapted thrice a week dialysis regime. These ‘excess weight gain adapted’ supplementary dialysis session prescriptions are only understood as punishment, resulting in fasting, opposition, and non-compliance, especially among adolescents. Protein wasting occurs partly as a result of decreased nutrient intake, however, other factors contribute to cachexia. This process of cachexia is favored in the state of chronic inflammation, metabolic acidosis, volume overload, and retention of uremic toxins. Malnutrition and cachexia could be limited by more intensive and more frequent dialysis regime. With conventional thrice a week dialysis regime, children have an inappropriately elevated cardiovascular morbidity and mortality mainly related to inadequate volume control, high blood pressure (BP) and left ventricular hypertrophy (LVH), to metabolic bone disease resulting in cardiovascular impairment (vascular calcifications), and to systemic inflammation. Applying strict dietary control of sodium intake, dry weight achievement and supplementary dialysis time, LVH may be improved in children on conventional HD. Nevertheless, in practice, children frequently have an elevated BP at start of the dialysis session. However, hypertension is not always related to overhydration and therefore is not always cured by probing a lowered dry weight. Conversely, more intensive and more frequent dialysis is almost always able to optimise volume control, i.e. hydration control and sodium control, and therefore to optimise BP control. Taken together, to the conventional thrice a week hemodialysis regimens alternative strategies should be developed.

Highly permeable membranes

Today, high-flux filters (highly permeable membrane) are used for the majority of children on conventional thrice a week dialysis regime. Due to their hydraulic permeability, internal filtration occurs into the membrane, with proximal filtration and distal back filtration in the dialysate, a process called internal hemodiafiltration. Due to the ultrafiltration control system of the machine, there is an apparently neutral fluid balance: the back filtrate dialysate is used as a substitution fluid to compensate the proximal dialyser filtration producing an undetermined convective flow. Therefore, the dialysate used with high-flux membranes should have the same purity of the on-line prepared substitution solution. The purity of the dialysis fluids, especially in terms of endotoxin count is of major importance for patient outcome, both in terms of morbidity and mortality. The addition of a determined convective flow to hemodiafiltration i.e. hemodiafiltration (Figure 1), offers several advantages: improved dialysis tolerance, especially reduced risk of hypotension, enlarged spectrum of uremic toxins dialytic removal, especially middle-sized uremic molecules, such as beta 2 microglobulin or phosphate, and controlled dialysis fluid purity. The amount of the convective volume is directly correlated to the patient’s outcome. There is a debate on the relative importance of the duration of the dialysis sessions on the one hand and on the other hand the weekly frequency of the dialysis sessions, but more frequent and more intensive hemodialysis offers more chance in quality of life if chronic long term hemodialysis is needed. Despite the general acknowledgement of the use of daily dialysis as rescue therapy, only very few pediatric dialysis programmes offers ‘daily dialysis for all’. One center experience of daily (6 days per week) in center on-line hemodiafiltration demonstrated impressive catch up growth (Figure 2), while growth is one of the best marker of adequacy of nutrition and dialysis in children. Daily hemodiafiltration allows anuric children to have normal food intakes for their age, only the day off dialysis potassium intake is restricted, no need or limited dose of potassium or phosphate chelators, and an optimised volume control, i.e. normal blood pressure without anti-hypertensive medication and no left ventricular hypertrophy. This more than 10 years in center intensive dialysis experience gives hope that chronic dialysis for anuric children does not restrict the chance of future outcome in terms of their final height or cardiovascular sequelae if applying a daily-complete dialysis dose, i.e. both a high Kt/Vurea diffuse dose and a determined high convective volume, i.e. the use of ultrapure dialysis fluids.

Michel Fischbach, Ariane Zaloszyc, Higel Laetitia, Strasbourg, France

S: 44: Delivery and quantification of dialysis
Room: HALL 2
Date: 03-06-2014
From 12:45 to 16:15
Different targets at different stages

Glycaemic control in the management of diabetes patients

Glycaemic control plays an important role in the pathophysiology of chronic vascular diabetic complications.

Prospective randomized controlled trials such as the Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes demonstrated that improvement in glycaemic control (target HbA1c 7%) resulted in a significant reduction in chronic vascular diabetic complications. The patients enrolled in this study were then followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) study for further 7 years (median follow-up period of 22 years in the combined studies); results showed that the previous intensive treatment of diabetes with near-normal glycaemia during the DCCT had an extended benefit on vascular complications and that early sustained intensive glycaemic treatment in patients with type-1 diabetes provides long-term beneficial effects.

Similarly in newly diagnosed patients with type-2 diabetes, the UK Prospective Diabetes Study (UKPDS) demonstrated that intensive glycaemic control (target HbA1c 7%) reduced the risk for the development of complications, and similarly to the EDIC study, a reduction in the risk for complications was observed during 10 years of UKPDS post-trial follow-up in those patients with improved glycaemic control.

On the contrary the ACCORD, ADVANCE, and the VADT trials enrolled patients with type 2 diabetes with approximately 10 years duration of disease, but poor glycaemic control (HbA1c ~9%), and at high vascular risk. One of the main questions asked by these studies was whether an intensive glycaemic control (HbA1c ~6.5%) had any significant effects on micro and macrovascular disease outcomes after a follow-up variable between 3.4-6 years. The results showed an overall failure on microvascular (and macrovascular) outcomes, likely to be linked to a poor ‘metabolic memory’, and possibly by the short duration of the follow up.

The UKPDS study demonstrated that even a reduction in HbA1c of 1% results in significant improvement in micro (retinopathy, nephropathy) and macrovascular (peripheral vascular disease, stroke, myocardial infarct, cardiovascular death) outcomes; further a history of good glycaemic control has been shown to significantly decrease the occurrence and speed of progression of chronic vascular complications.

Diabetic kidney disease affects 30-40% of patients with diabetes and represents the leading cause of end-stage renal failure in the western world.

When dealing with patients with diabetes, the clinician should be aware of important pathophysiological mechanisms, related to the decline in renal function, that are known to directly affect glycaemic control.

Indeed the kidney plays an important role in glucose whole body metabolism: the kidney is an important gluconeogenic organ (like the liver) especially in the post-absorptive state, and it plays a significant role in insulin metabolism.

Specifically, in patients with diabetes, progressive renal function decline results in important changes in glucose homeostasis that favour hypo- and hyperglycaemia, reduced gluconeogenesis and impaired insulin metabolisms lead to an increase in hypoglycaemic events, and to a secondary reduction of hypoglycaemic agents required to maintain euglycaemia (e.g. fall in insulin dose requirements).

Severe hypoglycaemia has been linked with increased mortality in patients with both type 1 and type 2 diabetes(1). Therefore as renal function decline progressively, hypoglycaemic treatment should be tailored to reduce the increased hypoglycaemic risk, and the linked cardiovascular morbidity and mortality, and a more flexible glycaemic target should be implemented. Important considerations should be addressed in relation to the glycaemic target in patients with diabetes on haemodialysis: a balance between intensive glycaemic control on one side, and increased risk of hypoglycaemia on the other side, should lead the clinician towards an individualised, tailored, target for each patients.

The individualised HbA1c target should be derived by taking into account safety (prevention of hypoglycaemic episodes), and by considering other factors such as diabetes duration, life expectancy, presence of comorbidities, established vascular complication, and the available resources(2).

A recent metaanalysis has proposed that, in patients with diabetes on haemodialysis, a HbA1c of more than 8.5% is paralleled by an increase in hazard ratio for death (mostly of cardiovascular nature) (3). Further, the same study suggested that in patients who have been on dialysis for 90 days or less, a HbA1c less or equal to 5.4% is also associated with an increased hazard ratio for death.

It is important to remember that the use of HbA1c, as a tool for assessing glycaemic control in patients on haemodialysis, does not accurately reflect the glycaemic control because of the shorter exposure of haemoglobin (related to the shorter red cells life) to the ambient glycaemia.

The use of HbA1c as a target for glycaemic control in patients with diabetes on haemodialysis is clearly not ideal, but currently represents the best available marker for glycaemic control in this population. Ideally determination of HbA1c should be replaced by continuous glucose monitoring, but to date studies are needed in this respect.

To make things even more complex, we are aware that many other variables could interfere on the glycaemic variability (hyper and hypoglycaemia) observed in patients on haemodialysis: the glucose concentration in the dialysate, the difficulties of patients in adjusting insulin doses on dialysis versus non dialysis days, or simply the general conditions of the patient before, during, and after dialysis.

In conclusion a tight glycaemic control is required to prevent vascular diabetic complications; as renal function declines, and the risk of hypoglycaemia increases, we are required to loosen the glycaemic control. When patients reach haemodialysis we should aim for a personalised target that takes into account many different parameters; more studies are warranted in the haemodialysis population to understand the best glycaemic target and its potential significance.

Luigi Gruendi, London, UK

5.45: Management of the diabetic patient with CKD

Room: AUDITORIUM

Date: 03-06-2014

From 12:45 to 14:15

References:

DaVita, a leading provider of kidney care with over 2,000 centers globally, recently signed a tender from the Kingdom of Saudi Arabia’s Ministry of Health to treat half of the nearly 10,000 patients currently under the Ministry’s care. It’s an important job; the prevalence of chronic kidney disease has accelerated faster in Saudi Arabia over the past three decades than in many parts of the world\(^1\), and the need for nephrologists committed to high-quality patient care has never been greater.

DaVita is looking for nephrologists to help us meet this challenge. These nephrologists will oversee outcomes, patient care, quality, safety, training and policies and procedures to pioneer a new age of kidney care in Saudi Arabia. Joining DaVita in Saudi Arabia could also include training as an interventionist in DaVita’s vascular access centers and the opportunity to build relationships with other world-class physicians while setting a new standard for clinical care and patient outcomes.

If you are looking to improve patient care and quality of life on a larger scale, DaVita would like to hear from you.

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Stop by the DaVita booth at ERA-EDTA or visit DaVita.com/SA.
A novel understanding

The role of epigenetics in kidney diseases

ike in many other common complex disorders, studies of chronic kidney disease (CKD) can make use of the increasing knowledge of the human genome, its variations and impact on disease susceptibility, initiation, progression and complications. Such studies are facilitated by novel readily available high through-put genotyping methods and sophisticated analytical approaches to scan the genome for DNA variations and epigenetic modifications. Epigenetics (literally in addition to the genetic sequence) is a discipline that for many years has languished in the shadow of its genomic big brother. Although epigenetics is considered a relatively novel research area the term dates back about 65 years ago. Implementation of epigenetic methods into novel clinical practice may contribute to novel understanding about the effects of the toxic uremic milieu in the complicated uremic phenotype (Fig 1). The epigenetic state, i.e. potentially reversible changes in genetic information other than the primary DNA sequence, determines whether a particular gene, or other genetic elements, will be in an active or repressed state in terms of transcriptional activity or repression. DNA-methylation is critical to maintain junk DNA in a transcriptionally silent state. Epigenetic states modifying the genome and direct gene programs, include DNA-methylation of CpG dinucleotides, nucleosomal histone modifications and other mechanisms. With the rapidly increasing insights into basic mechanisms of epigenetics, it is now becoming possible to better understand the mechanisms whereby environment and lifestyle influence disease development. It is also possible to study how the various cell-type specific functional genomes are differently geared to respond to various cues from a dynamic environment. A loss of this phenotypic plasticity is likely one of the important factors behind many diseases. As a genetically determined degree of variability in the epigenetic state may be important for disease development the ability or propensity to have an epigenetic alteration as a result of environmental challenges may be genetically determined. Studies on the epigenome may help to decipher molecular mechanisms and to define novel dietary and pharmacological treatment strategies for uremia-related pathogenic processes.

The uremic milieu affects the epigenotype

Recent studies have shown that epigenetic disturbances are important in a number of human diseases, such as cancer, psychiatric disorders and obesity. Our understanding of epigenetic mechanisms in CKD is still lagging, and further studies are needed to understand the importance of aberrant DNA methylation in relation to the unphysiological impact of the uremic milieu on the functional genome, organismal metabolism and the associated disconnection between chronological and biological vascular age. Although most interest has focused on aberrant DNA methylation in the context of uremia areas of epigenetic regulatory mechanism beyond this, such as histone modifications and RNA interference definitely require further studies. However, in the context of uremia DNA methylation is of particular interest, as common uremic derangements, such as hyperhomocysteinemia, inflammation, dyslipidemia and oxidative stress, have been shown to associate with altered DNA methylation homeostasis. Among these common metabolic alterations, hyperhomocysteinemia and persistent inflammation may be the most important drivers of aberrant DNA methylation. As global DNA hypomethylation is correlated to hyperhomocysteinemia and persistent inflammation has been related to global DNA hypermetylation the total changes in DNA methylation status may be a matter of balance. It is evident that measurement of aberrant global DNA methylation is very unspecific (like measuring fever in infectious conditions) and in future studies changes in gene specific methylation should rather be measured. Recent studies have shown different methylation pattern comparing diabetic patients with and without nephropathy and differences in methylation of genes involved in fibrosis, oxidative stress and inflammation are observed in CKD patients with no or fast progression. Thus, epigenetic modifications may be an important tool to predict disease susceptibility and rate of kidney function loss. It is also likely that epigenetic dysregulation in uremia contribute to the unacceptable high cardiovascular risk in this prematurely aged population. Further research is needed to study the association between aberrant global DNA-methylation, gene-level methylation status, and the silencing (or activation) of candidate genes associated with atherosclerosis and vascular calcification. Moreover, as uremic toxins (such as p-cresyl sulfate and indoxyl sulfate) was shown to induce DNA methyltransferase (DNMT) protein expression, which silence the key phosphate regulator KLOTHO via hypermethylation, this opens a new window for epigenetic targeting of specific genes related to complications of CKD. Despite these findings this exciting research area is still in the early discovery phase and further site-specific methylation analyses are needed to gain more detailed knowledge of epigenetic regulators in CKD.

Dysregulated epigenome as a cause of obesity

The ongoing global pandemic of obesity and metabolic syndrome has important implications for not only cardiovascular disease (CVD) but also CKD. In fact, although obesity is a complex phenotype, it may be one of the most important preventable causes of CKD. As genetic associations as such do not explain more than about 2% of changes in BMI, gene-environment interactions may represent the most important regulators of obesity risk. This should increase the attention to epigenetic processes. Indeed, genes associated with obesity risk are susceptible to epigenetic alterations and obese patients have an epigenetic pattern different from non-obese subjects. It was recently demonstrated that increased BMI is associated with methylation of the locus of hypoxia inducible transcription factor (HIF3A) in both blood cells and adipose tissue. Thus, as studies link changes in the epigenome to risk of obesity, further studies of life-style and diet on the
epigenome are of much interest. Indeed, a long-term high-fat diet decreases the methylation of the MCR-4 receptor gene, which could stimulate appetite. Moreover, a recent study showed that acute exercise affects the epigenome via promoter hypo-

methylation and increased muscular expression of PGC-1α, PDK4, and PPAR. As epigenetic modulations, like DNA and histone methylation, are stable enough to be transmitted to future generations, and epidemiological studies suggest that the eating habits could affect disease risk in future generations the impact of our parents and grandparents lifestyle and eating habits on the risk of overweight, CKD and CVD deserve further studies.

Treatment of a dysregulated epigenotype

When consistent changes in the epigenome (such as DNA methylation) have been characterised in relation to variations of the uric acid phenotype this could allow nephrologists to identify high-risk CKD individuals for both kidney disease progression and premature cardiovascular disease. Epigenetic targeting of specific genes may become an effective strategy to prevent progression of uremia-related CKD. The effects of various epigenetic-targeted and pathway-targeted therapeutic approaches on unbalanced DNA methylation, gene silencing, and vascular health and outcomes should be investigated further. However, targeting the epigenome with drugs, such as DNMT inhibitors and histone deacetylase inhibitors, in CKD patients is probably not realistic within the near future and the only definite conclusion that can be made at this time point is that substantial additional work is needed in this exciting area.

Peter Stenvinkel, Stockholm Sweden

No complete reversal of risk factors

Endothelial dysfunction in kidney transplant recipients

The arterial endothelium is a monolayer of cells that carries out multiple important tasks. Endothelial dysfunction is seen in a variety of pathological conditions, with atherosclerosis being the most prominent. It is also found in patients with hypercholesterolaemia, diabetes, hypertension, chronic kidney disease, heart failure, cigarette smoking, and aging. Blood vessels dilate in response to shear stress, a process called flow-mediated vasodilation (FMD); measurement of FMD is a clinical method for evaluating endothelial function. Impairment of FMD is seen in the early stages of atherosclerotic vascular disease.

While endothelial dysfunction is associated with impaired clinical outcomes, tests of endothelial function are not currently recommended for use as surrogate markers in clinical practice. Improvement of endothelial function is a desirable therapeutic goal, and several therapeutic interventions have shown promise in this regard. However, only a few of these (i.e., statins) have been systematically assessed in large, prospective, randomised, controlled studies.

Chronic kidney disease (CKD) is one of the major risk factors for the development of cardiovascular disease (CVD). In addition to the well-recognised risk factors, these patients have additional risk factors such as vascular calcification, inflammation, and increased oxidative stress.

Two distinct vascular pathologies co-exist in CKD: atherosclerosis and arteriosclerosis. Atherosclerosis is a disease of the intima characterised by calcified fibro-atheromatous plaques, which ultimately rupture causing vascular occlusive events. Furthermore, endothelial dysfunction (ED), which is present even in the early phases of CKD, seems to be an important factor for the development of accelerated atherosclerosis. ED is an independent risk factor for future cardiovascular events, the major cause of mortality in CKD. Although the improvement in ED after kidney transplantation has been shown in some studies, the mechanisms have not been clarified yet.

Endothelial dysfunction is an early event in atherosclerosis and is linked to inflammatory processes in the vasculature. A hallmark of endothelial dysfunction is impaired endothelium-dependent vasodilatation, which can be identified both invasively in the coronary arteries and noninvasively in peripheral vessels. Reduced bioavailability of endothelial nitric oxide (NO) is one key mediator. Normally, on chemical (i.e., acetylcholine and bradykinin) or mechanical (i.e., increased blood flow or shear force) stimuli, the endothelial NO synthase in the endothelial cells is activated; the endothelial act diffuses basolaterally to vascular smooth muscle and induces vasodilatation. NO has numerous other antiatherogenic properties, including inhibiting leukocyte and platelet adhesion and smooth muscle proliferation.

The vascular endothelium is recognised as having multiple complex functions which regulate vascular tone, thrombosis, haemostasis, permeability and cell adhesion. It releases vasodilatory substances such as nitric oxide (NO), prostacyclin, C-type natriuretic peptide and endothelium-derived hyperpolarizing factor, as well as vasoconstrictors including endothelin-1 (ET-1), angiotensin II (Ang II) and thromboxane A2. Endothelial dysfunction or, more correctly ‘endothelial activation’, is considered a key initiating step in atherogenesis and also contributes to arterial stiffening (arteriosclerosis). Traditionally, ED due to chronic inflammation and oxidative stress is thought to be an early and important feature of CKD.

Endothelial dysfunction has been implicated as one of the chief pathological mechanisms contributing to the association of CVD and CKD and may, in part, explain the strength of the graded correlation between worsening renal function and increasing CV risk. There remains however, a lack of clinical studies examining ED in subjects specifically with reduced GFR, particularly in those with early-stage CKD.

The FMD improves with transplant which is in keeping with large clinical observations on improvement of cardiovascular mortality and morbidity with kidney transplantation. This might be related to recovery from uraemia-related, non-traditional risk factors with transplantation. Also interestingly, the patients with transplantation do not have a normal FMD, which indicates, with transplantation, risk factors are not completely reversed. The residual renal function abnormality, side effects of immuno-suppression and the historic damage due to uraemia prior to transplantation continue to contribute towards cardiovascular damage. Thus transplant patients though having a better quality of life and improved survival, still have a higher cardiovascular mortality compared to general population.

Some studies show that the strong predictable association exists between hs-CRP, Asymmetric dimethyl arginine (ADMA), Pentraxin-3 (PTX-3), tumour necrosis factor-like weak inducer of apoptosis (TWEAK) and endothelial dysfunction in CKD patients and renal transplant recipients. Further studies incorporating a larger number of patients to evaluate influence of the other markers of oxidative stress, inflammation and NO metabolism and endothelial cell activation on the cardiovascular system in CKD patients and renal transplant recipients are desirable.

Mahmut Ilker Yilmaz, Ankara, Turkey

S 49: Cardiac risks in kidney transplant recipients

Room: EULICUM 2
Date: 03-06-2014
From 14:15 to 16:00

References


Peter Stenvinkel

Mahmut Ilker Yilmaz © Yilmaz

Peter Stenvinkel © Stenvinkel

S 50: Genetics and Epigenetics in hypertension and CKD
Room: EULICUM 1
Date: 03-06-2014
From 14:15 to 16:00

The arteriolar endothelium is a monolayer of cells that carries out multiple important tasks. Endothelial dysfunction is seen in a variety of pathological conditions, with atherosclerosis being the most prominent. It is also found in patients with hypercholesterolaemia, diabetes, hypertension, chronic kidney disease, heart failure, cigarette smoking, and aging. Blood vessels dilate in response to shear stress, a process called flow-mediated vasodilation (FMD); measurement of FMD is a clinical method for evaluating endothelial function. Impairment of FMD is seen in the early stages of atherosclerotic vascular disease.

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Mahmut Ilker Yilmaz, Ankara, Turkey
Non-invasive tool for detection and monitoring

Micro RNAs in renal injury

I nflammation in transplanted kidneys is one of the primary causes of acute kidney injury. It is associated with severe morbidity and mortality and thus represents a major socioeconomic health problem. It is a consequence of a variety of different injurious insults in native kidneys (e.g., during cardiac surgery). Moreover, it is commonly associated with the transplantation procedure and thus an unavoidable phenomenon in transplanted kidneys (1).

Reperfusion associated with additional cellular injury

During ischemic acute kidney injury a transient drop in blood flow to the kidney is followed by a reperfusion period. Reperfusion itself, though vital to a restoration of kidney function, is associated with significant additional cellular injury. We have recently summarised the deleterious effects and thus serve as powerful no-
Micro-RNAs and diabetic kidney disease

Accumulation of extracellular matrix (ECM) proteins such as collagens (fibrosis) and mesangial expansions (hypertrophy) in the kidney glomerulus are our targets as major features of diabetic nephropathy (DN) especially in the early stage. TGF-β is induced by diabetes in mesangial cells (MC) via upstream stimulatory factors through promoter E-boxes. Engagement of TGF-β to its receptors induces the phosphorylation and nuclear translocation of Smad transcription factors, which regulate TGF-β-induced gene expression. TGF-β plays a key role in mesangial fibrosis by increasing the expression of ECM proteins such as collagen and fibronectin. TGF-β also activates Akt kinase through inhibition of Pten to induce hypertrophy. Although many approaches have attempted to clarify the mechanisms of DN, there were still black boxes in signal transduction initiated by TGF-β (Figure 1). micro-RNAs (miRNAs), short (about 22 nucleotides) non-coding RNAs, are identified as new players in the pathogenesis of human diseases including renal diseases. miRNAs negatively regulate the target genes through their 3' untranslated region (3'UTR). Significant changes of the expression of miRNAs cause abnormal expression of target genes related to many kinds of diseases. Interestingly, the connections between targets and miRNAs open the black boxes in signal transductions and lead to discovery of new pathways. For example, ECM accumulation related to renal fibrosis by TGF-β was explained by increase of collagens by down-regulation of E-box repressors (ZEB1/2) targeted by miR-192 (also miR-200 family) induced by TGF-β (Figure 1 box 1) (1). Activation of Akt related to glomerular hypertension was explained by inhibition of Pten by miR-216a/217 cluster or inhibition of FOG2 (PI3K inhibitor) by miR-200 family (Figure 1 box 2) (2). The second interesting aspect is the cascade of miRNAs. miR-216a/217 cluster and miR-200 family members have E-boxes in the upstream genomic regions and regulated by ZEB E-box repressors which are targeted by miR-192 (Figure 1 Box 1 & 2), the same regulation of collagen (1-3). Therefore, miR-192 controls several miRNAs which amplifies signaling. Those cascades may be involved in acceleration of TGF-β signaling and chronic kidney diseases like DN (2, 3). The third interesting aspect is signal circuits mediated by miRNAs. An example is autoregulation of miR-192 promoter by acetylation of histone and transcription factors (such as Ets-1) through p300 activation by Akt (Figure 2) (3, 4).

Figure 1: Opening black boxes in signal transductions in DN by miRNAs (and their cascades). High glucose (HG) conditions induce TGF-β which causes DN through fibrosis (extracellular matrix protein (ECM) accumulation) and hypertrophy (Akt activation). There were black boxes in TGF-β-induced signaling in DN. Box 1 explains how TGF-β increases ECM like collagens through miR-192 (and miR-200) and E-box repressors (ZEB1/2). There is a cascade from miR-192 to miR-200 family members. Box 2 explains how TGF-β activates Akt through miR-216a/217/200 family and Pten or FOG2 related to hypertrophy. There are two cascades from miR-192 to miR-216a/217 cluster and to miR-200 family. Those miRNA cascades may amplify the signal transduction and may be involved in chronic kidney diseases like DN.

Figure 2: Signal circuit mediated by miR-192. Initially miR-192 is upregulated by TGF-β through Smad activation (phosphorylation). Increase of miR-192 activates Akt as described in Figure 1 box 2. Akt kinase phosphorylates and activates p300, a histone acetyltransferase, which acetylates histones and transcription factor Ets-1. The acetylation of histones and transcription factors creates open chromatin of the promoter region of miR-192 and further enhances expression of miR-192. This signaling circuit mediated by miR-192 may be involved in acceleration of signal transduction and chronic kidney diseases like DN. HG, high glucose; Ac, acetylation; P, phosphorylation. ©Kato

References
A shift from discovery to implementation

Proteomic analysis: what’s new?

Proteomic biomarkers carry the hope of improving patient management by enabling more accurate and earlier detection of renal disease, but also of defining the most suitable therapeutic targets. Kidney disease has been a focus of attention for clinical proteomic studies, owed in part to the fact that urine appears to be an excellent target for proteomics, due to its easy accessibility, stability, and moderate complexity.

Several studies based on single urinary (protein) biomarkers have demonstrated association of these biomarkers with chronic kidney disease (CKD), but also with acute kidney injury (AKI). However, these studies in general also demonstrate a lack of specificity of the single biomarkers: for example NGAL was described as a biomarker for AKI, for CKD, and also for several other diseases. These observations have supported the development of multi-marker panels that potentially better ‘capture’ the complexity of ongoing pathological processes for optimised accuracy in the assessment of disease.

In several studies the value of the multi-marker concept has shown significantly superior performance in comparison to single markers e.g. in the early detection of AKI, of CKD, and in the prognosis of disease progression. These studies also indicated that multi-marker concepts are associated with initially higher costs. Specifically available (e.g. RAAS blocking agents) demonstrate benefit at late stage of the diseases, and while their benefit in early stages has been advocated, it has yet to be proven.

Collectively, these facts have resulted in the initiation of first proteomic biomarker guided intervention trials. The PRIORITY trial (www.eu-priority.org), outlined in Figure 1, is a multicentric intervention study in 3280 patients, aiming at demonstrating the benefit of low dose spironolactone treatment at an early stage, specifically guided by a panel of 273 urinary peptides in the prevention of diabetic nephropathy. If positive, this trial would indicate benefit of proteomics guided intervention, hence fulfill the demands stated above.

The advancements in proteome analysis have also resulted in approaches to decipher the molecular pathology of kidney diseases, employing Systems Medicine approaches. This is the central aim of several multicentric European projects, e.g. SysKid (www.syskid.org) or iMODE-CKD (www.imodeckd.org). Based on the finding that complex diseases result in the change of multiple molecular parameters likely caused by multiple insults, Systems Medicine aims at deciphering these multiple significant molecular changes, and combining them into a comprehensive in silico model. These projects are currently ongoing, but first results are already available.

While several proteomic biomarkers have been described to be of superior performance in the assessment and prognosis of kidney disease, they are generally not implemented. Especially in CKD this appears to be to a large degree a result of the demand to assess benefit based on hard endpoints, which generally can only be assessed in a timeframe of 10 or more years, when aiming at early detection and intervention. As such, an open issue is if currently research in CKD biomarkers is even relevant: if the biomarkers will not be implemented (as a result of the inability to demonstrate benefit on a hard endpoint), then there is no need for research in this direction. A solution to the absence of hard endpoints in prospective studies in CKD proteomics would be employing prospectively collected samples with long term follow-up potentially available in biobanks. Unfortunately the current biobanks generally do not serve this need. Frequently information on the samples in the biobank is not publicly available, and access to samples is not transparent (samples are not provided), although the biobanks were funded with public money. The establishment of biobanks that allow access to the information on the material available and that implement transparent procedures on how samples are made available would be of enormous benefit.

Clinical proteomics is beginning to deliver tangible results in the field of kidney disease, and first classifiers based on proteomic biomarkers have matured to a degree that they are applied in clinical studies and in clinical assessment of patients. Systems Biology, based on proteomics, and also on other omics technologies, begins to emerge as a promising approach to enable understanding of disease on a molecular level. This holds the potential of identifying superior therapeutic targets.

These advances have resulted in a shift of the field, from discovery towards actual implementation, and identifying novel challenges. Currently, there is no useful guidance on the definition of a reliable (protein) biomarker, the required performance of such a biomarker and the type of studies required to achieve implementation. Guidance on these issues appears a worthy cause for the relevant professional societies, ideally in close collaboration with the involved scientists. Such guidance could include defining the ideal context-of-use and recommendation for study designs to test the biomarkers’ practical value, all aiming at the ultimate goal, to effectively translate research into benefits for patients.

Harald Mischak, Hannover, Germany

S36: The novel uremic toxins: what did we learn recently?

Room: HALL 2
Date: 03-06-2014
From 8:00 to 9:30

Figure 1 Design of the proteomics-driven PRIORITY intervention trial to interfere with development of diabetic nephropathy. Underlying assumptions are that 20% of normoalbuminuric patients (diabetes duration 5–10 years) will show pathophysiological changes indicative for early stages of diabetic nephropathy. Targeted therapeutic intervention with spironolactone will reduce the development of microalbuminuria during a period of 3 years in this selected cohort from 35 to 25%. To demonstrate significant benefit ($\alpha=0.05$, $\beta=0.8$), a total of 3280 patients will be screened, of these 656 being at risk will be randomized.
Hyperkalemia: Old Foe with New Faces
Invitation to the ZS Pharma CME lunch symposium at the ERA-EDTA 2014 Congress, Amsterdam

Date: Monday, June 2, 2014, 13:15 – 14:45
Meeting Room: G102-103 RAI First Floor

Purpose of Activity
The activity will review the clinical significance of chronic hyperkalemia in chronic kidney disease (CKD) and also in other settings in which renin-angiotensin-aldosterone system (RAAS) inhibitors are crucial agents. This information describes the expanding patient profile for developing hyperkalemia. Further recent observations provide clearer information on the inflection point above which the risk of mortality rises demonstrably in pre-dialysis CKD as well as in patients on dialysis. This information defines the risk stages of hyperkalemia. Lastly, at least two new oral therapeutic agents are emerging that may provide more reliable and selective reductions in potassium absorption and thus allow alternatives to the now-common practice of reducing or eliminating RAAS inhibitors in those with CKD and other risk states that benefit from them. Strategies such as these should mitigate the risks of hyperkalemia without eliminating the benefits of RAAS inhibition. Clinicians need current information about hyperkalemia’s clinical epidemiology, risk stages and emerging treatment options.

Educational Objectives
After completing this activity, the participant should be better able to:
1) Develop knowledge of the expanding disease states that are most at risk for developing hyperkalemia.
2) Identify the clinical thresholds for rising mortality in patients with hyperkalemia and chronic kidney disease.
3) Develop awareness of recent clinical trials in controlling hyperkalemia.

Target Audience
This activity has been designed to meet the educational needs of Nephrology professionals involved in the care of patients with kidney disease.

Physician Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of CFMC and The Med Ed Group, Inc. CFMC is accredited by the ACCME to provide continuing medical education for physicians.

CFMC designates this live activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Agenda and Faculty

13:15 Lunch

13:45 Introduction by Programme Chair
Peter A. McCullough, MD, MPH, FACC, FACP, FAHA, FCCP, FNKF
Baylor University Medical Center, Baylor Heart and Vascular Institute
Baylor Jack and Jane Hamilton Heart and Vascular Hospital
Dallas, Texas, USA

13:50 Current Epidemiology of Hyperkalemia
Csaba P. Kovesdy, MD
Fred Hatch Professor of Medicine in Nephrology
Director, Clinical Outcomes and Clinical Trials Program
Division of Nephrology, University of Tennessee Health Science Center
Memphis, Tennessee, USA

14:05 Hyperkalemia and Cardiorenal Disorders
Peter A. McCullough, MD, MPH, FACC, FACP, FAHA, FCCP, FNKF

14:20 Standard and Emerging Treatment
Professor David Goldsmith, MB, BCHir, FRCP, FASN, FERA
Consultant Nephrologist
Guy’s and St Thomas’ Hospitals
London, UK

14:35 Panel Discussion Session

14:45 Closing Remarks by Chairperson

There is no fee for this educational activity.
Beyond metformin and before insulin

The role of hypoglycemic agents in the treatment of patients with type 2 diabetes mellitus and CKD

About 20–30% of the typical nephrologist’s patients will have type 2 diabetes mellitus (T2DM), usually with associated diabetic nephropathy. Patients are commonly referred from the endocrinologist to the nephrologist at CKD Stage 3–5, and pose a number of additional treatment problems compared to patients with normal renal function.

Thiazolidinediones (TZD)
TZDs are peroxisome proliferator-activated receptor γ activators. They reduce hepatic glucose production and improve insulin sensitivity in skeletal muscles. They are the most commonly studied second-line anti-diabetic drugs in CKD (pioglitazone 4 studies, rosiglitazone 7 studies, troglitazone 1 study), and have found to be effective, with a fall in HbA1C of 0.5–1.5%. As with non-CKD patients, oedema is a recognised side effect, but beneficial effects have also been noted: a fall in blood pressure, reduced triglycerides, C-reactive protein, and improved endothelial function.

These drugs have however been the subject of considerable regulatory interest. Troglitazone has been withdrawn from the market due to hepatic side effects. Pioglitazone has been found to be associated with bladder tumours and has been withdrawn in some countries. Rosiglitazone has been withdrawn from many markets due to reports of increased risks of myocardial infarction and death, but the FDA has recently lifted its earlier restrictions after the RECORD randomised clinical trial failed to show an increased risk. Studies in CKD have been conflicting. One study (Brunelli et al. 2009) showed an increased risk of death for TZDs in patients simultaneously treated with insulin, but a reduced risk in non-insulin treated patients. Ramirez et al. (2009) noted a 59% increased risk of cardiovascular death associated with rosiglitazone, while Schneider et al. (2008) found a 40% fall in cardiovascular events and death associated with pioglitazone patients. These findings suggest that pioglitazone is the preferred drug in this class for CKD patients.

Dipeptidyl peptidase IV (DPP-4) inhibitors (‘gliptins’)

The incretin hormones GLP-1 and GIP are secreted from intestinal endocrine mucosal cells in response to food intake, and are responsible for 70% of insulin response after food intake. In addition to their insulinitropic effects, they reduce appetite, inhibit gastric emptying, decrease glucagon production and slow the rate of glucose production, all desirable goals in DM, particularly in ESRD where glucagon levels are raised. Their function is reduced in T2DM. CKD patients without DM have a normal incretin production, but a reduced incretin effect, suggesting a reduced β-cell response to incretin in CKD.

DPP-4 inhibitors are oral drugs that block the enzyme that inactivates incretins, and lead to increases in active GLP-1 and GIP. They are weight neutral and do not cause hypoglycemia. A number of possibly beneficial effects have been noted, including reduced insulin resistance, reduced leptin and IL-6 concentrations, increased adiponectin levels and modified adipocyte differentiation, reduced VEGF-induced angiogenesis and antiproliferative effects.

Sitagliptin, vildagliptin and saxagliptin have each been studied in CKD patients and have been found to be effective, with a HbA1C fall of 0.3–0.8%, although saxagliptin was found to be ineffective in patients with ESRD. No side effects were seen. Sitagliptin, vildagliptin, alogliptin and saxagliptin all require dose reduction in CKD, but this is not the case with linagliptin. These drugs are often combined with metformin in one formulation; these formulations should be avoided in CKD due to differing dose requirements.

Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

These drugs (exanatide, liraglutide & lixisenatide) mimic the effects of endogenous incretins. Thus, they will stimulate insulin production proportionally to glucose, suppress glucagon production, slow gastric emptying and decrease appetite. They do however require injection. Their main advantages are absence of hypoglycemia, and weight loss. However, delayed gastric emptying leads to nausea and vomiting, which may be a particular problem for malnourished ESRD patients. Pancreatitis is a rare complication for both DPP-4 inhibitors and GLP-1 RA. Exanatide dose is reduced in CKD, and its use is not recommended in patients with CKD5, while liraglutide does not require dose reduction.

These drugs are expensive and experience in CKD is limited.

Other Drugs

Acarbose and miglitol are α-glucosidase inhibitors of intestinal glucomylase, glucosucrase and maltase, leading to delayed polysaccharide metabolism and postprandial absorption of glucose. Intestinal glucose absorption is not however affected. Gastrointestinal side-effects are common, Acarbose is contraindicated with severe uremia, and experience with miglitol in CKD5 is limited. Dapagliflozin, canagliflozin and empagliflozin are sodium glucose co-transporter 2 (SGLT2) inhibitors which reduce glucose reabsorption in the proximal tubules, causing glycosuria. Since their effect is dependent upon significant renal function, its use in nephrology is generally limited to patients with CKD 1 & 2.

Conclusion

The nephrologist should concentrate upon the avoidance of side effects, particularly hypoglycemia. Antidiabetic drugs may interact with each other, increasing the risk of hypoglycemia. Sulphonylureas in particular should be reduced in multidrug regimes. Many physicians may prefer to avoid drugs which are renally excreted, in order to avoid toxicity, while some may consider this an advantage, particularly when using expensive gliptide or GLP-1 RA therapy. In the absence of economic considerations, linagliptin’s easy dosage and side effect profile is attractive, while sulphonylureas offer a cheaper alternative.

References

Brunelli et al. (2009) showed an increased risk of death for TZDs in patients simultaneously treated with insulin, but a reduced risk in non-insulin treated patients.

Ramirez et al. (2009) noted a 59% increased risk of cardiovascular death associated with rosiglitazone.

Schneider et al. (2008) found a 40% fall in cardiovascular events and death associated with pioglitazone patients.

These findings suggest that pioglitazone is the preferred drug in this class for CKD patients.
DaVita, a leading provider of kidney care with over 2,000 centers globally, recently signed a tender from the Kingdom of Saudi Arabia’s Ministry of Health to treat half of the nearly 10,000 patients currently under the Ministry’s care. It’s an important job; the prevalence of chronic kidney disease has accelerated faster in Saudi Arabia over the past three decades than in many parts of the world, and the need for nephrologists committed to high-quality patient care has never been greater.

DaVita is looking for nephrologists to help us meet this challenge. These nephrologists will oversee outcomes, patient care, quality, safety, training and policies and procedures to pioneer a new age of kidney care in Saudi Arabia. Joining DaVita in Saudi Arabia could also include training as an interventionist in DaVita’s vascular access centers and the opportunity to build relationships with other world-class physicians while setting a new standard for clinical care and patient outcomes.

If you are looking to improve patient care and quality of life on a larger scale, DaVita would like to hear from you.

Grow your career with DaVita in Saudi Arabia. Stop by the DaVita booth at ERA-EDTA or visit DaVita.com/SA.
Chances and challenges

Genome-wide association studies in nephrology

Despite evidence for a genetic component, the identification of risk genes for complex renal diseases has been difficult until recently. A new technique, genome-wide association studies (GWAS) enabled remarkable progress in the field of complex genetic kidney diseases over the past 5 years. GWAS have been used to identify genetic risk variants for end-stage renal disease, stage III chronic kidney disease, IgA nephropathy, diabetic nephropathy, focal segmental glomerulosclerosis, membranous nephropathy, and microalbuminuria.

The prevalence of chronic kidney disease (CKD) in adults ranges between 5 and 10% in many countries. CKD is a complex disease resulting from the interplay of adverse environmental influences and genetic risk variants in many genes. Regardless of its etiology, CKD is defined according to the KDIGO Guidelines based on the sustained presence of reduced glomerular filtration rate (GFR) and/or increased albuminuria. It represents a common final path of different renal and/or systemic diseases.

The first GWAS for the identification of common complex diseases have been conducted less than 10 years ago. GWAS almost always require large study populations for the successful identification of genetic risk variants, because the individual contribution of a single common genetic risk variant to the overall disease risk is usually moderate or small. In order to carry out a GWAS, millions of genetic markers, single nucleotide polymorphisms (SNPs) are genotyped using the DNA-enriched library technique known as mapping by admixture disequilibrium analysis. Such studies have yielded novel insights into the genetics of complex diseases by which disease alleles across different kidney disease etiologies may give rise to important insights in kidney disease genetics in the past decade. In two different patient populations, African American individuals with non-diabetic end-stage renal disease and patients with FSGS, risk variants in the MYH9/APOL1 were identified. Based on the large magnitude of the conferred risk and the higher prevalence of the risk alleles in individuals of recent African ancestry, it was estimated that the risk alleles explain up to 70% of the excess risk of kidney disease observed among African Americans. Intriguing data suggest that the responsible risk alleles reside in APOL1 and rose to high frequency in Africa because they confer a selective advantage against trypanosomiasis, but more research into the molecular mechanisms of how the APOL1 risk alleles cause renal disease is needed. Careful examination of the effect of the genetic variants across different presumed etiologies of kidney disease has led to the insight that APOL1-associated kidney disease extends across etiologies such as hypertension, FSGS and HIV nephropathy and that grouping individuals by risk variant carrier status has a clear relationship to kidney disease progression.

Because GWAS are forward genetic screens and as such carried out in an unbiased fashion with respect to the identity of the associated genes, little is known about the function of the associated genes and about their relationship to kidney disease. The newly identified gene variants provide promising new targets for functional studies not only to understand the function of the genes and their relationship to kidney disease but also to improve our understanding of pathways underlying different forms of kidney disease and of renal physiology in general. Future research will be directed towards gaining a better understanding of the allelic spectrum and consequences of kidney disease risk variants as well as their utility for disease classification and prediction. A more complete set of risk alleles will be attained by the extension of the study of complex kidney diseases to incorporate rare alleles by integrating GWAS findings with those obtained from whole exome or whole genome sequencing of the same individuals. Conversely, studies of monogenic familial forms of disease can be extended towards the search for more common modifier alleles via these same techniques. Advances in genome annotation outside of transcribed genes and across a variety of different cell types will improve our understanding of the underlying mechanisms by which disease alleles across the frequency spectrum confer risk.

The examination of identified genetic risk variants across different kidney disease etiologies may give rise to improved disease classification and may have implications for prediction and treatment. With the much accelerated pace of gene discovery, translating the consequences of genetic risk variants into an understanding of the molecular mechanisms of disease and the identification of potential therapeutic targets likely remains the biggest challenge in the years to come.
The right drug in the right dose

The link between renal allograft dysfunction and cardiovascular risk

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in renal transplant recipients. The annual rate of fatal or non-fatal CVD events is 50-fold higher than in the general population. Prior to transplantation many patients are already exposed to multiple risk factors for CVD. Following transplantation additional risk factors further contribute to the overall risk. It is also known that the Framingham risk model underestimates CVD risk in the renal transplant population. Especially uremic cardiomyopathy is assumed to be an important risk factor that impacts on survival after transplantation. Based on the data from the ALERT trial in 2012 a cardiovascular risk calculator for renal transplant recipients was developed (Soveri I et al.). This seven-variable model included renal function (creatinine) next to age, previous coronary heart disease, diabetes, low-density lipoprotein, number of transplants, and smoking as risk factors. One year later the model was validated with the data from BENEFIT and BENEFIT-EXT (Soveri I et al.).

Given the fact that renal dysfunction is an independent predictor for CVD in renal transplant recipients it is important to consider the impact of factors that compromise renal function, including ischemia-reperfusion injury, rejection and immunosuppression related toxicity. At present studies are ongoing to reduce ischemia-reperfusion injury, either by intervening with machine perfusion strategies, or with pharmaceutical interventions.

Rejection and immunosuppression are the focus of clinical trials, aiming to give the right drug in the right dose to each individual patient.

Late-breaking clinical trials

Yesterday’s session provided brand-new information in various fields of renal medicine.

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Study data presented on Sunday cover a broad range of topics relevant in the treatment and prognosis of chronic kidney disease.

➤ Promising experimental agent in diabetics (Hermann G. Haller, Germany): In type II diabetics, chronic kidney disease (CKD) is accompanied by chronic, systemic inflammation, oxidative stress and progressive loss of renal function. Thus, any therapeutic approach to slow or even stop CKD progression and, thus, to avoid renal replacement therapies, would be a milestone in nephrology. Emapticap pegol (NOX-E36) specifically binds and inhibits the pro-inflammatory chemokine CCL2. In the phase-II study presented by Hermann Haller on Sunday, the substance proved to be harmless in nephrology.

➤ Blood transfusion in CKD may contribute to heart failure (Brian Bradbury, USA): In recent years, the use of red blood cell (RBC) transfusion for the treatment of CKD-related anemia has increased. However, transfusion expands the extracellular volume and little information about the harms of this treatment is available. Indeed, hospitalization is common in patients with advanced CKD, according to a study presented by Brian Bradbury: 1,381 out of 7,829 individuals with stage 4 or 5 CKD were hospitalized with a diagnosis of heart failure during follow-up; 1,082 cases had at least one week of follow-up. For these cases, 39,029 control periods were included in the analysis; 0.7% of cases and 0.1% of control periods had been exposed to transfusion. This corresponded to an increased risk ratio of 13.4 (95%CI: 5.4-33.2), controlling for confounding attenuated the effect, although risk remained elevated.

➤ Canagliflozin is safe and effective in type 2 diabetes with reduced GFR (Ronan Rousset, France): Canagliflozin is a novel oral antidiabetic agent of the group of gliifozins, which are selective inhibitors of the sodium glucose co-transporter (SGLT2) in the proximal renal tubules. Gliifozin treatment lowers renal reabsorption of glucose and leads to glucose excretion in the urine. In addition to lowering blood sugar, it reduces body weight and blood pressure. Potential side effects of canagliflozin are mainly associated with the increase in urinary glucose content. In addition, a transient decrease in glomerular filtration rate (GFR) was observed in phase III studies. The new data of Ronan Rousset and his team indicate that canagliflozin is effective in type 2 diabetes with eGFR reduction during treatment. Moreover, canagliflozin was generally well tolerated in this group of patients, with a low incidence of volume depletion-related adverse events across groups.

➤ C-reactive Protein outperforms cystatin C for all-cause mortality (David Warnock, USA): When assessing the risk of all-cause mortality, estimated glomerular filtration rates calculated on the basis of cystatin C (GFRCys) outperform those based on creatinine (GFR Crea); GFRCys, however, fails in predicting the complications associated with CKD. On the other hand, inflammation biomarkers like C-reactive protein (CRP) are strongly associated with early deaths.

The analysis presented compared the performance of cystatin C and CRP quartiles in assessing the risks for all-cause mortality among participants in the REGARDS study. Elevated CRP was strongly associated with early deaths in the REGARDS cohort, and significantly outperformed cystatin C for predicting all-cause mortality during the first two years of follow-up.

➤ Dental health as a prognostic factor (Giovanni Strippoli, Italy): Oral diseases may contribute to a worse prognosis in CKD patients. Now, Strippoli et al. have shown in their multinational cohort study with more than 4,000 dialysis patients, that dental health is an independent risk factor for mortality in this group of patients: Brushing teeth, flossing and changing the tooth brush every three months was linked to a better outcome. The study results might encourage dialysis patients to intensify oral hygiene.

From left: Hermann Haller, Germany; Brian Bradbury, Thousand Oaks, USA; Ronan Rousset, France; David G. Warnock, Birmingham, USA; Giovanni Strippoli, Bari, Italy.

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Today’s Late-breaking Clinical Trial Session
Room: Hall 2
From: 8:00 to 9:30

The right drug in the right dose by intervening with machine perfusion strategies, or with pharmaceutical interventions.

Rejection and immunosuppression are the focus of clinical trials, aiming to give the right drug in the right dose to each individual patient.
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