Baxter and Gambro have become one. Two of the world's leading renal care companies taking a bold leap forward. With our combined strengths, we'll deliver a stronger portfolio of products and therapies to advance the state of renal care around the world.
“I see a great future ahead”

Interview with Prof. Raymond Vanholder, President of the ERA-EDTA

Raymond Vanholder is most optimistic about the development of ERA-EDTA: “With all these promising projects and collaborations, I see a great future ahead for our society,” he states in this interview.

As the President of the ERA-EDTA, can you explain what the mission of the society is?

Prof. Vanholder: Our mission is to promote nephrology on the clinical, the scientific, and the political level. Nearly all the society’s activities serve that aim. The Annual Congress, the CME courses, the fellowships, as well as the many research programmes and networks – they all strengthen clinical nephrological practice and research. In addition, we have many networks and initiatives that raise political and public awareness of kidney disease.

The number of ERA-EDTA members is continuously increasing – is this due to a good marketing strategy, or does it reflect the growing importance of this sub-specialism in the field of internal medicine?

Prof. Vanholder: I guess it is both.

On the one hand, public awareness of kidney disease, especially chronic kidney disease (CKD), has improved and this also adds to the strong reputation of our profession. Nephrology is being talked about and is one of the key disciplines within internal medicine. Many physicians in related disciplines, such as cardiology, rheumatology or diabetology, have realised its importance, and the numerous networking projects of the ERA-EDTA foster such interdisciplinary collaboration. The ERA-EDTA has become more visible as a result, even for non-nephrologists, and many doctors have joined us. The rise in membership is also due to our excellent marketing, however. We have been working very much on our visibility – and I would like to thank all the staff at the ERA-EDTA headquarters in Parma and especially Monica Fontana Faughnan, our External Relations Manager, for their superb work. Special offers and packages have been created to facilitate membership for young nephrologists and for specialists from low income countries. Communication has also been improved – and that is a big incentive for becoming a member of a medical association nowadays. Our members do not just receive the journals, NDT and CKJ, but are also kept informed about latest developments by “Follow us” and the electronic newsletter, “Follow us Flash”, as well as through social media like Facebook and Twitter.

Looking back, what have been the greatest successes of the ERA-EDTA over the past three years?

Prof. Vanholder: Well, that is a difficult question to answer right now, because it is often only years later that one sees if something has turned out to be a success or not. Nevertheless, there is quite a list of initiatives and projects we have initiated or collaborated on, and which are great achievements for our society. Our collaboration with the European Kidney Health Alliance (EKHA), for example, is very fruitful and has proved to be a big success in promoting kidney health within the European Parliament. Other important achievements include the alliance with EuroPD to strengthen peritoneal dialysis, which is still under-represented throughout Europe, and the creation of the Young Nephrologists’ Platform (YNP). The latter is of great importance, because taking care of the young clinicians and scientists is an investment in the future. The strategy to extend the society’s activities (fellowships, CME courses etc.) beyond Europe also seems promising, and I am pleased that we have established or revived contact with the ASN, the ISN and the Nephrologists´ Platform (YNP). The ERA-EDTA Registry has also been improved – and that is a big incentive for becoming a member of a medical association nowadays. Our

Continued on page 3
EURODOPPS is born!

A newly established joint venture will bring together the strengths of DOPPS and the ERA-EDTA Registry.

On Friday, ERA-EDTA and Arbor Research signed a collaboration agreement for the creation of EURODOPPS. This newly established joint venture will bring together the strengths of two initiatives in collecting and analyzing epidemiological data on patients with chronic kidney disease (CKD) in Europe – the Dialysis Outcomes and Practice Patterns Study (DOPPS) and the ERA-EDTA Registry. During the agreement signing ceremony, Prof. Vanholder, President of the ERA-EDTA, pointed out that the new partnership is clearly a milestone: “It will enhance science and research. Therefore we are really proud to announce this important joint venture.”

The ERA-EDTA Registry collects epidemiologic data from the national and regional renal registries in Europe and countries bordering the Mediterranean Sea with the purpose of performing scientific research and reporting statistics on dialysis and kidney transplant patients in Europe. In particular, the Registry studies disease patterns, treatment and patient outcomes in the various member countries. The DOPPS is a prospective cohort study of hemodialysis practices in more than twenty countries on four continents. DOPPS uses a common data collection protocol over time, and thus is able to monitor the impact of changes in clinical practice patterns and policies on patient outcomes. EURODOPPS data will include seven countries: Germany, Italy, France, United Kingdom, Belgium, Spain, and Sweden.

What will be the advantages of EURODOPPS? The formal partnership with ERA-EDTA and regular transfer of EURODOPPS data to the Registry will enhance the use of these data to address scientific and policy questions that are of interest to the ERA-EDTA, the European nephrological community and health care authorities. It will facilitate research by European investigators and the comparison of results from EURODOPPS and the ERA-EDTA Registry. With time, the possibility may be explored to extend this data-base with the help of the European Union to more European countries and to therapies other than hemodialysis, for example transplantation. For the purpose of conducting and supervising research, a special EURODOPPS Oversight Committee has been created. “This partnership is a further valuable and complementary contribution to the ERA-EDTA Registry that celebrates its 50th anniversary this year,” explained Dr. Kitty Jager, Director of the ERA-EDTA Registry. “Changes in European policy and clinical practice guidelines, as well as the introduction of new products, will undoubtedly influence dialysis practices and EURODOPPS will help to effectively monitor this changing landscape to ensure that patients on chronic hemodialysis in Europe continue to receive the highest standards of care. The new alliance might also provide a further credible data source to inform health care authorities about the current state of European dialysis care.”

The National Society Village

15 national renal societies and associations are presenting their activities in Hall 1.

National renal associations play an important role in the transfer of scientific results into patient care on a local level. In order to promote their visibility in the European context, the ERA-EDTA supported the launch of the National Society Village already at last year’s Annual Meeting in Istanbul. This year, 15 national societies take the opportunity to present themselves as part of the National Society Village – their booths in hall 1 were designed to provide a friendly atmosphere that brings visitors together and invites them to scientific discussions.

“For many questions, for example when establishing national registries or planning clinical studies, national organizations can benefit from each other – exchanging scientific ideas, results and best-practice examples is crucial for success and may also help to bundle activities. Therefore, the ERA-EDTA constantly collaborates with the national societies to foster this kind of networking. The National Society Village is only one example of our activities in this field, we also organize yearly meetings such as the last one in Würzburg, which was extremely fruitful,” says Professor Christoph Wanner, Chairman of the ERA-EDTA Registry and Council Officer. “And not to forget, the National President’s Dinner at the Congress provides another opportunity for representatives of national societies to discuss national needs and network with councilors of the ERA-EDTA.”

The National Society Village

Room: Hall 1, Area A3, A4 and B13
Date: 05-31-2014 to 06-02-2014
Continued from page 1

Chinese Society of Nephrology. There are two projects I am especially proud of: the first is our collaboration with the "Lancet". This highly-renowned journal will publish a special issue on nephrology, and the papers will be discussed at the Congress in two joint symposia. The other very fruitful alliance is the one with "EURODOPPS". The ERA-EDTA registry has been very active in establishing this collaboration and we are very happy that the agreement has just been signed, name... on Friday last. With all these promising projects and collaborations, I see a great future ahead for our society.

During your presidency, networking has always played a major role. Why is that so important in nephrology? Prof. Vanholder: Networking drives science forward. People meet, discuss ideas and allow their scientific projects to cross-fertilise. We have seven active working groups, many research programmes, as well as international or interdisciplinary projects – and each one influences all the others. A multi-dimensional network has thus been established and it is increasing the impact of nephrological research.

Furthermore, networking strengthens our political and public influence. It is also due to such networks that ERA-EDTA has become a society. It is also due to such networks that ERA-EDTA has become a society. It is also due to such networks that ERA-EDTA has become a society. It is also due to such networks that ERA-EDTA has become a society. It is also due to such networks that ERA-EDTA has become a society.

What is it that fascinates you most about nephrology? If you were a student, would you still choose to become a nephrologist? Prof. Vanholder: I have never regretted the choice I made. Nephrology is intellectually very demanding and inspiring. Personally, I have a strong scientific interest in the progression of fibrosis and renal failure, which is very complex, but nephrology offers many other interesting research topics. And it is a very satisfying subject on the clinical level, too. We are the only sub-specialism that is able to replace an organ function over a long period, for years or even decades. By doing so, we save the lives of our patients day in, day out.

Not only transplantation, but also dialysis allows people to survive a life-threatening disease with a rather good quality of life – this is something that we, and sometimes also the patients, tend to forget.

No reliable marker available

Biomarkers in focal segmental glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is a podocyte-derived glomerular disease and comprises genetic forms as well as primary and secondary forms. FSGS is a pattern of histological injury rather than a disease and the separation of the forms is difficult. Primary FSGS is a progressive disorder with a 50% ESRD rate over 8 years in patients who do not respond to therapy. Moreover, the disease recurs in 30% of patients who receive a kidney transplant. Genetic forms of FSGS do not recur after transplantation.

It is now well-accepted that the pathogenesis of primary FSGS involves a circulating factor that disturbs podocyte function and increases glomerular permeability. The urokinase-type plasminogen activator receptor (uPAR) has important functions in cell migration. uPAR can be shed from the cell membrane resulting in soluble uPAR (suPAR).

There had been great expectations that suPAR is a permeability factor that causes and clearly influences the clinical course of primary FSGS, but they were not fulfilled. Ethnic differences in suPAR levels were described: Lower levels were measured in a Chinese population, and Huang et al. published the overlapping of suPAR values between primary FSGS and other glomerulopathies. In 2013, a single-center report from Chicago was published which did not find any correlation between suPAR levels and FSGS or other glomerular diseases in 110 children. In 2014, three subsequent reports in Kidney International doubted the significance of suPAR as a diagnostic biomarker for FSGS. Different forms of suPAR may exist. Probably the responsible suPAR for FSGS is not measured.

To sum up, a reliable biomarker which could distinguish between primary and secondary FSGS and between FSGS and other glomerular diseases is not available. Elevated serum suPAR levels occur in about half of all cases of children and adults with nephrotic syndrome, but also in other proteinuric glomerular diseases. Serum suPAR levels assessed by ELISA do not correlate with proteinuria and are not able to predict the relapse of proteinuria. The significance of suPAR in genetic forms of FSGS is unclear. Furthermore, nowadays there is no reliable marker to predict the therapeutic response and to differentiate minimal change disease from FSGS. Patients with two NPHS2 mutations (and other unambiguous genetic forms of FSGS) should not be treated with immunosuppressive drugs, only rarely the response to cyclosporine was mentioned. Surely, new prospective multicentric studies with uniform data and a new ELSA kit for suPAR are necessary.

Jana Reiterová, Prague, Czech Republic

S 46: Novel biomarkers in glomerular diseases

Room: ELICUIUM 2
Date: 03-06-2014
From 12:45 to 16:15
Dr. Tilman B. Drüeke started his nephrological activities more than 40 years ago and worked essentially at Necker Hospital in Paris (France) where he started to work on a post-doctoral fellowship in 1969, after having studied in Germany, where he was born. At Necker, he also headed an INSERM research unit. After having reached his emeritae in 2009, he followed his co-worker Dr. Ziad Massy to the Amiens University Hospital. He was scientifically active in a broad range of topics related to nephrology with main interests in β2-microglobulin and its relation to dialysis-related bone disease, the chronic kidney disease / metabolic bone disease complex, hemodialysis and its cardiovascular complications, renal anemia and hypertension.

He was involved in a large number of important clinical trials. He was Chief Editor of Nephrology, Dialysis and Transplantation and Associate Editor of the clinical Journal of the American Society of Nephrology. At this moment he is Associate Editor of Kidney International. In addition, he served on the Executive Board of Kidney Disease: Improving Global Outcomes (KDIGO) and was chair of the KDIGO guidelines on CKD/MBD. Dr. Drüeke authored and co-authored more than 500 original publications, several ones of which in major journals.

Like Dr. Drüeke, also Dr. London started his nephrological activities more than 40 years ago and he also worked essentially in Paris, at Manhes Hospital where he became chief of the nephrology/hemodialysis department in 1971 until his retirement in 2009, although he graduated in Medicine at Charles University in Prague, then Czechoslovakia. He was senior researcher at INSERM. He was President of the ERA-EDTA from 2008 to 2011 and is currently chair of EURECA-m, one of the ERA-EDTA Working Groups. He received several awards and honorary memberships. He was scientifically active especially in the study of cardiovascular disease in Chronic Kidney Disease and the mechanisms inducing vascular calcification and stiffness in this condition, especially the changes in the bone-vascular axis.

Dr. London authored and co-authored more than 350 original publications, of which several ones in major journals and these publications have abundantly been cited. In contrast to the two other laureates, during his entire career Dr. Murer was not active as a nephrologist but as a basic researcher. After having obtained a degree in biology in Fribourg, Switzerland, he obtained a PhD in biochemistry in Zürich, Switzerland, and moved to the Max Planck Institute in Frankfurt, Germany, in 1975 to join the renal physiology laboratory. Then he returned to the biochemistry department in Fribourg, and became professor at the university of Zurich from 1981 on, where he was head of the renal physiology department. He became vice-president for Medicine and Sciences at the University of Zurich (2006-2010) after which he moved to the emeritae. He was President of the “Deutsche Nephrologische Gesellschaft”, President of the Swiss Society of Nephrology, Councilor of the International Society of Nephrology (ISN), and co-chair of the ISN Forefronts Programme in which function he introduced the Nexus programme in 2006. He was chair of the programme committee of the 2003 World Congress of Nephrology in Berlin. In 2010 he was elected co-Chair of the ERA-EDTA Scientific Advisory Board (SAB), a position that he still maintains.

He served on the editorial board of several major journals, was Chief Editor of Pfluegers Archiv / European Journal of Physiology, and still is associate editor of the journal Physiology. He received several awards among which the Homer Smith award and the Donald Seldin award. He is member of the Swiss Academy for Medical Sciences. Dr. Murer authored and co-authored more than 450 original publications, several ones of which in major journals. The three laureates of today, Drs. Drüeke, London as well as Murer, are true giants of European nephrology who stood at the basis of a broad array of clinical and scientific information that has its repercussion today and will continue to impact nephrology for many coming years.

Alexander M. Davison received the Award for outstanding contributions to ERA-EDTA

Dr. Davison became a member of ERA-EDTA in the 1970’s and served the society in many different functions. He first became Associate Editor of the EDTA Proceedings in 1981, becoming Editor the next year. In 1985 the Council decided to replace the EDTA proceedings by an official journal, and he was appointed to accomplish the transition and became the first Editor in Chief of the new journal that was named Nephrology Dialysis Transplantation. After the end of his term as Editor in Chief in 1996, he was elected Council member of ERA-EDTA in the same year, and then became President of the Society in 1999 which he remained till 2002. As this period coincides with the improvement of the accessibility of East Europe, he played a key role in organizing educational activities in that part of Europe, in part in collaboration with the International Society of Nephrology (ISN).

Under his Presidency also the ERA-EDTA Registry took another direction by starting a collaboration with the Amsterdam Medical Center (AMC) in the Netherlands in 2000, which subsequently avowed itself as a very fruitful and rewarding move. He was instrumental in ensuring financial stability to the society, together with Vincenzo Cambi. He also negotiated for the first joint ERA-EDTA/ISN congress in Berlin in 2003. He further started cooperation with other European scientific societies like the European Society for Artificial Organs (ESAO) and the European Kidney Research Association (EKRA). Finally, he was the first President to install brainstorming sessions among the Council, an activity that persists until today, allowing to plan in advance future moves and activities of the Society.

He was appointed NDT Emeritus Editor in 1993; awarded a Honorary membership of ERA-EDTA in 2002 and became Distinguished Fellow of ERA-EDTA (FERA) in 2011.

His impressive list of actions has been the basis for the ERA-EDTA’s current successful activities and the present ERA-EDTA Officers are extremely fortunate to be able to build further on this.

Finally, Dr. Davison has been active as a respected clinician with in addition a solid scientific curriculum with a large number of highly appreciated publications in peer review journals, books and several honorary doctorates.

Rafael Kramann won the Young Investigators Award

Dr. Kramann accomplished the largest part of his career at Aachen University in Germany but is currently working as a post-doctoral research fellow Brigham and Women’s Hospital (Boston, USA). Next to being MD and PhD, he also obtained a degree in Good Clinical Practice training and a principal investigator licence for clinical trials. He ended among the top 1% of the German Medical State Examination to obtain the licence to practice medicine. He received 7 awards and obtained 4 grants for a total amount above 350,000 EUR. His research focuses essentially on stem cells, uremic vasculopathy, and myocardial fibrosis.

In spite of his young age (he is only 32), he published in total approximately 30 original publications, most of which in renowned journals.
Individualization of HD therapy – the way to address clinical challenges

Chairman’s Welcome and Introduction
Claudio Ronco, Vicenza, Italy

Who benefits from HDF and why, based on recent clinical trials?
Paul Cockwell, Birmingham, UK

How to prevent intradialytic hypotension while reducing volume overload
Rajiv Agarwal, Indianapolis, IN, USA

Dialysis standard of care for high bleeding risk HD patients – what the HepZero study tells us
Maurice Laville, Lyon, France
Mechanisms of increased left ventricular mass

Inflammation, endothelial dysfunction markers and increased LVM in hypertensive predialysis CKD patients

Little is still known about the mechanisms of increased left ventricular mass (LVM) in patients with chronic kidney disease (CKD). However, left ventricular hypertrophy is a strong risk factor for cardiovascular events and mortality in CKD and reduction of left ventricular mass (LVM) could reduce the risk for these events, both in hypertensive patients and in patients with stage 5 CKD on dialysis. Therefore, understanding these mechanisms is essential for designing novel therapeutic strategies to attenuate cardiovascular disease in CKD patients and improve outcome.

Renal failure predisposes for increased cardiovascular disease through changes in plasma components, changes in endothelial structure and function, as well as due to pressure and volume overload. These changes may result in vascular injury and endothelial dysfunction and trigger an inflammatory response. Both inflammation and endothelial dysfunction are known important players in the atherosclerotic process and by thus may contribute to the increased cardiovascular burden in CKD patients.

Our study

For the first time this longitudinal study was performed to investigate the association of inflammation markers and endothelial dysfunction markers with LVM indexed for height$^{2.71}$ (LVMI) in hypertensive predialysis CKD patients. For this study, 206 incident consecutive adult patients were included from the outpatient CKD clinics of two hospitals in Greece. The inclusion criteria were both the presence of CKD and hypertension. The inflammation markers included C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα), whereas the endothelial dysfunction markers were intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Both CRP (mg/l) and LVMI (g/height$^{2.71}$) were assessed annually for three years. Linear mixed modeling was used to examine the longitudinal association between the inflammation markers and endothelial dysfunction markers with LVMI. All analyses were adjusted for the potential confounders age, sex, primary renal disease, smoking, history of cardiovascular disease, HDL/LDL ratio, and the use of ACE/ARBs, fibrates, diuretics, aspirins, and statins.

The three main findings and the interpretation of these results:

1. The inflammation score vs inflammation markers separately
   The results of this study showed an association of the inflammation score based on CRP, IL-6 and TNFα with LVM taking potential confounders into account. It seems that combination of such markers into one score better predicts adverse outcomes in CKD patients than single markers alone. It is likely that, although inflammation markers may partly represent a similar process, they may also represent different parts of the inflammation process and may therefore have a complementary role in detecting inflammation.

2. Differences between early vs late CKD stages
   Our results further suggest that the association of the inflammation score with LVMI was pronounced in CKD stages 1-3, while it was absent in CKD stages 4-5. Consequently, inflammation could be suggested as part of the mechanisms for increased LVMI in this patient group, in CKD stages 1-3. In contrast, in CKD stages 4-5 other factors that relate to the more severe decrease in renal function such as volume overload, hypertension aggravation, hyperphosphatemia and hyperparathyroidism probably dominate and possibly play a more important role towards the increased LVMI.

3. VCAM-1 vs ICAM-1
   In our study it was shown that VCAM-1, but not ICAM-1, was associated with LVMI. VCAM-1 therefore seems to have a more crucial role than ICAM-1 in both mechanisms leading to increased LVMI, i.e. atherosclerosis and hypertension.

Adult stem cells and regenerative medicine

Hans Clevers, President of the Royal Netherlands Academy of Arts and Sciences, gives the second Plenary Lecture

One of the world’s leading researchers on stem cells and their potential for regenerative therapy, Hans Clevers, tomorrow will hold the plenary lecture on “Adult stem cells and regenerative medicine”. Clevers obtained his Ph.D. in 1985 at Utrecht University and was a professor in immunology there from 1991 to 2002, when he became director of the Hubrecht Institute for Developmental Biology and Stem-Cell Research at the Royal Dutch Academy of Sciences. In March 2012, he was elected as President of the Royal Netherlands Academy of Arts and Sciences. Hans Clevers has continued to be a member of the Royal Netherlands Academy of Arts and Sciences since 2000 and a member of the American Academy of Arts and Sciences since 1996. The most important scientific achievement in his career was the identification of stem cells in the intestine. He was the first investigator to identify them. Subsequently his team purified these stem cells and studied their characteristics.

The Royal Netherlands Academy of Arts and Sciences describes him in a portrait: “Hans Clevers is seen as an enthusiastic, engaged, and inspiring researcher who is one of the world leaders in his field. His research deals with the intestine, in both its healthy and diseased state. He has discovered that there are numerous similarities between the normal process whereby intestinal tissue is renewed and the development of intestinal cancer. Improved understanding of these processes is crucial to developing new ways of treating cancer. Hans Clevers has described the molecular signalling pathways that are disrupted by cancer and has identified a protein that is specific to stem cells in the intestine. He has then been able to grow ‘mini-intestines’ from individual stem cells. These are the first steps on the road to regenerative medicine, in this case the regeneration of intestinal tissue.” Clevers is the recipient of several prestigious awards, including the Breakthrough Prize in Life Sciences in 2013.
A proof of friendship
Joint Symposium of CSN and ERA-EDTA

The cooperation with other societies plays an important role during the ERA-EDTA meetings every year. An important example of the good international relationships and a demonstration of the friendship to nephrologists in Asia is the Joint Symposium of the Chinese Society of Nephrology (CSN) and the ERA-EDTA that is already an inherent part of the congress every year.

Learning from each other

Nephrologists in Asia and in Europe may have to deal with the same diseases, yet the challenges and the approaches to solve problems can be very different. Therefore the joint meeting is a possibility to reflect on the own methods and to learn from each other.

This time the session gives the congress participants a possibility to look at serious kidney diseases from an Asian and a European point of view. Chaired by CSN President Zhi-Hong Liu and ERA-EDTA Chairman Norbert Lameire, the session will focus on Acute Kidney Injury (AKI) and Lupus Nephritis. Bi-Cheng Liu will discuss the impact of AKI in China (article on page 15), whereas Lameire will reflect on the epidemiology of AKI in Europe (article on page 14). His talk will be followed by a lecture on Lupus Nephritis in China which will be delivered by Guo-Hua Ding. Vladimir Tesar (article on page 16) will highlight the relevance of Lupus Nephritis in Europe.

Input from America

ASN highlights: the newest findings on important topics

It is a good tradition that during the ERA-EDTA Congress partner organisations are invited to present their newest findings on important topics.

Translational projects on Acute Kidney Injury

In the session “ASN Highlights” Ravindra Mehta will deliver the Acute Kidney Injury lecture. He will present summaries of current translational projects in a hypothesis-driven format. New clinically important findings are also described and then measured against contemporary evidence-based standards of practice.

Karen Griffin will deliver the Hypertension lecture. Differences in patient susceptibility to hypertensive renal injury are presented as background for the approach to treatment. Current approaches to blood pressure (BP) measurement and the use of available antihypertensive agents in achieving recommended BP goals are discussed.

Rapid review on Chronic Kidney Disease

Michel Chonchol will deliver the Chronic Kidney Disease lecture. This session provides a rapid review of the pathophysiology and treatments of nephrotoxins, non-glomerular kidney disorders, including diabetic kidney disease, acid-base/electrolyte disorders, and nephrolithiasis. In addition, the epidemiology and newer data regarding renal cystic disorders and masses are reviewed.

The organizing committee is very pleased to announce the fourth ERA-EDTA Renal Run, which will take place on Sunday, June 1st, 2014 at 15:00.

This year runners will enjoy a 3 km run through Beatrixpark, which is located very close to the Amsterdam RAI Congress Center.

Beatrixpark, one of the nicest parks in Amsterdam, was created in the years 1936-1938. It was originally designed as a “romantic” park, but after the 2nd World War, Beatrixpark was redesigned into a more modern and functional style. Today, the Beatrixpark is a green area behind the Amsterdam RAI; it is a local park - nice, clean and quiet. The oldest part of the park is the nicest one, as it kept its original romantic style influenced by English parks - with a small lake and open landscape. This particular part of the Beatrixpark received the status of the city monument in 2005. Runners will definitely enjoy the surroundings during this time of the year.

Participants will be divided into categories according to age and gender. Registration is free, but it must still be done online for administrative purposes NO LATER THAN Saturday, May 31 at 17:00. Onsite registration will be also possible on Sunday, June 1st until 13:00 at the ‘Renal Run Info Desk’ that will be situated in the Amsterdam RAI.

Each participant will receive a number and a t-shirt. Refreshments will be provided after the run. Cloakrooms will be available at the Amsterdam RAI.

We are looking forward to your participation and wish you a very enjoyable and fun experience.
Current immunosuppressive treatment has improved kidney-allograft survival, albeit at the expense of reduced immunosurveillance to viruses. Consequently, viral infections are increasingly observed in renal transplant recipients. T cells play a critical role in the immune response to viral pathogens. Persistent human cytomegalovirus (CMV) infection leaves a clear imprint in the immune system, consisting of a strong increase in the number of circulating virus-specific, effector-type CD8+ T cells. These points will be addressed:

- Phenotypic and functional characterization of CMV specific CD8+ T cells are in a resting state and have a low proliferation and low death rate. They may exert direct cytolytic activity making them typical effector-type cells. This population increases with age and in situations of immunosuppression. Their main function is to maintain latency to immune-evasive CMV.
- The molecular pathways involved in the induction and maintenance of CMV-specific effector-type cells, in particular the changes in their transcriptome.
- Lymph node compartment: CMV seropositive renal transplant recipients have more circulating total CD8+ T cells, a high percentage of which can be directed against just one CMV epitope. Data will be shown regarding the relationship between this large circulating pool and populations residing in the lymph nodes, regarding both functional characteristics and clonal heterogeneity.
- Heterologous immunity: Because memory T cells generated in response to a (viral) pathogen can also recognize allo-antigens, so called heterologous immunity, we studied to what extent circulating CMV-specific T cells recognize allo-antigens of donor-origin in kidney transplant recipients.

For patients with established renal failure, renal transplantation remains a treatment and not a cure. One of the unfortunate complications, particularly in transplant recipients with a primary renal disease of primary glomerulonephritis, is post-transplant disease recurrence (PTDR), that is the original disease which caused the native kidney to fail, returning in the renal allograft. Recurrent glomerulonephritis is the third most common cause of renal allograft loss. Despite this, the current literature is full of conflicting information as to the risk of graft loss secondary to PTDR. There are a number of reasons for this; small sample sized studies due to the relative rarity of the disease at the individual centre level, varying definitions of PTDR, differences in study design i.e. clinical diagnosis versus histological confirmation of disease recurrence etc. all of which have led to inconsistent results. Although the majority of international and national guidelines recommend living donor transplants in primary glomerulonephritis there is no real consensus as to whether the donor type, i.e. living versus deceased donor, influences the risk of graft loss from PTDR. Therefore we aimed to quantify the relative risk of graft loss from PTDR and determine if the risk of graft loss altered with donor type.

For this study we used the ERA-EDTA Registry database to assess the survival outcome of renal transplant patients where the original disease was one of 5 different primary glomerulonephritides; Immunoglobulin A Nephropathy (IgAN), Membranoproliferative Glomerulonephritis (MPGN) type I and MPGN type II, Membranous Nephropathy (MN) and Focal Segmental Glomerulosclerosis (FSGS). We included a total of 13,514 first renal transplants from 17 European national or regional registries in the study. Survival analysis by means of cumulative incidence competing risk method and Cox regression were performed on all adult first renal transplants between 1991 to 2010 and followed until 31st December 2011. The main outcome was graft failure, defined as a return to dialysis and censored events were death with a functioning graft or loss to follow up. We performed two separate multivariable Cox regression analyses firstly we compared each glomerulonephritis group to a control group. The control group was all first renal transplants where the native renal disease was Autosomal Dominant Polycystic Kidney Disease (ADPKD), with the assumption that any additional risk of graft loss as compared to ADPKD (in which the original disease cannot recur) was due to PTDR. In the second model within each glomerulonephritis group we compared living donor (with the subgroup living related and living unrelated donors) to deceased donor transplants. Adjustments were made for time on dialysis prior to transplantation, age at transplantation, gender, country and era of transplantation.

In the study, we found that patients with primary renal disease of primary glomerulonephritis had a higher relative risk of graft failure compared to ADPKD. IgAN had an equi-valent relative risk of graft failure as compared to ADPKD in the first 5 years post transplantation after which the relative risk of graft failure exceeded that of ADPKD. This finding is in line with other recent studies with longer term follow up which have also shown that despite its reputation as an indolent disease post transplant disease recurrence in IgAN does eventually have a detrimental outcome on renal allograft function.

The expected survival advantage normally seen in living donor kidney transplants compared to deceased donor transplants was present in IgAN, Membranous nephropathy and FSGS but not in MPGN type I or II. Living donor transplants as compared to deceased donor transplants in those with a primary renal disease of FSGS had a lower relative risk of graft failure (particularly, as we found, in living related transplants). Further living donor transplants in MPGN I and MPGN II did not have a worse outcome than the corresponding deceased donor transplants.

The results of this study could aid in advising potential transplant recipients and donors of the potential rates of graft loss particularly when considering donor type.
Alexion Satellite Symposium at the 51st Congress of the European Renal Association – European Dialysis and Transplant Association

Diagnostic challenges in thrombotic microangiopathies

Sunday 1 June 2014, 18:45–19:45

Chair: Professor Dirk Kuypers, Department of Nephrology and Renal Transplantation, University of Leuven, Belgium

Venue: Room G102-103, first floor

Programme

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<td>18:45–18:55</td>
<td>Welcome and introduction to TMA</td>
<td>Dirk Kuypers</td>
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<td>19:20–19:40</td>
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<td>19:40–19:45</td>
<td>Conclusion and Q&amp;A</td>
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A buffet dinner will be served after the symposium.

Register for the symposium

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Well-known disease, but many unknown variables

*Tuberculosis: Still a major problem in the post–transplant period*

**Issue 2 / June 1, 2014**

**ERA-EDTA**

Tuberculosis is still a major problem in the post-transplant period for various reasons:

- Its incidence is very high corresponding to a 27-fold increase in transplant patients as compared to the general population. Also, prevalence of tuberculosis in transplant recipients may reach even up to 10-15% in developing countries.
- Stereotypes of mechanisms take place in the pathogenesis (i.e.: reactivation of latent infection, acquisition of new infection after transplantation, transmission from the donors and nosocomial acquisition), it may be unavoidable.
- There are therapeutic problems, as well, because:
  1. There is a defective immune response due to chemical immunosuppression.
  2. Interactions of antituberculosis drugs with immunosuppressants may result in unpredictable serum levels of both groups of drugs.
  3. Since many of these patients suffer from liver problems, and since all of them get many other medicaations, drug toxicities are quite frequent.
  4. Increasing drug resistance is a major problem in these cases.

Post-transplant tuberculosis is a major cause of morbidity. There is an increased risk of rejections, and up to 25% of graft loss have been reported in some series. The main reason for this complication is the interaction between the rifamycins and calcineurin inhibitors (CNI) and/or mTOR inhibitors (mTORI), which results in a dramatic decrease in the serum levels of the latter drugs. Post-transplant tuberculosis may be a major cause of mortality as well; mortality rates even up to 30% have been reported in the literature. Patients with disseminated infection, prior rejection episodes, receipt of ATG are defined to be the predictors of mortality.

Regarding the clinical presentation, the vast majority of the typical clinical findings of tuberculosis (i.e.: cough, bloody sputum, fever, loss of appetite, weight loss, night sweats) in the immunocompetent patients may be absent in the immunocompromised hosts. One third to half of transplant cases are admitted with disseminated or extrapulmonary tuberculosis. Also, pyomyositis, skin ulcers, abscess formation, tenosynovitis, tuberculosis lymphadenitis are quite frequent. Fever may or may not be present, and the patients may be admitted with fever of unknown origin. Most cases appear within the first year posttransplant.

Considering diagnosis, although clinical findings, tuberculin skin testing, interferon-gamma release assays (IGRAs), imaging techniques, nucleic acid and molecular testing, sputum examination for staining and culture are very useful in the immuno-compotent host, this is not the case for immunosuppressed cases.

From the clinical point of view, tuberculosis is pauci-symptomatic and extrapulmonary tuberculosis is more common in transplant recipients. Tuberculin skin testing may be negative in up to 70% of the patients, and IGRA may be less sensitive in immunosuppressed. Imaging techniques are also mostly non-diagnostic; cavities are quite rare, atypical presentations such as focal infiltrate, miliary pattern, nodules, pleural effusions, interstitial infiltrates are common. Not infrequently, sputum smear results are negative despite active disease. Nucleic acid amplification tests are less sensitive in sputum-smear-negative populations. Therefore, most of the time invasive techniques (such as fiberoptic bronchoscopy, mediastinoscopy, laparoscopy, tissue biopsies) are required for diagnosing tuberculosis in transplant recipients.

**Treatment of active tuberculosis**

In general, the management of tuberculosis is considered under two headings: management of active tuberculosis and latent disease. Actually, drugs do not differ between these two entities; however the protocols are completely different.

Medications for treatment of active tuberculosis are classified as first line (isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin) and second line drugs (kanamycin, amikacin, rifabutin, levofloxacin, ethionamide, cycloserine and capreomycin). Combinations of these drugs are used for longer periods as compared to routine daily treatment of infections.

In the immunocompetent patients the standard protocol is using isoniazid and rifampicin for 4 months (continuation phase), followed by isoniazid and rifampicin for 4 months (phase). In the case of multidrug-resistant tuberculosis (which is quite rare in the newly diagnosed cases) microorganism is resistant to at least isoniazid and rifampicin, the two most potent antituberculosis drugs; hence treatment is more problematic. Of note, proposed treatment protocols are mainly based on RCT in immunocompetent hosts; thus, data in transplant recipients are quite scarce and of low quality.

Regarding the duration of the treatment, there are many controversies. Some authors suggest that six months of treatment may be adequate if the regimen contains rifampicin, while some others suggest at least nine months of treatment. Of course, local resistance patterns and epidemiologic as well as susceptibility data from the individual patient’s isolate should be considered.

There are major controversies with regard to the selection of the regimen. As an example: The American Society of Transplantation underlines that a rifamycin-containing regimen is mandatory in all cases, because of its potent sterilizing activity and preventing the emergence of resistance. However, the Spanish Society of Infectious Diseases and Clinical Microbiology (GESITRA) reserves usage of rifamycins only to severe cases. This protocol suggests 2-drug regimens [isoniazid and ethambutol (or pyrazinamide)] for 12–18 months as an alternative. Streptomycin is generally avoided because of its nephrotoxicity.

All protocols underline the interaction of rifampin with CNI and mTORI. Decreased levels of the latter two increase the risk of rejection episodes. As a result the vast majority of the protocols suggests a 3–5 fold increase in the dose of CNI or mTORI and also monitoring serum levels very closely, because CYP3A4 induction by rifampin takes several days to occur, usually peaks within a week, and lasts for days to weeks. The dosage of steroids should be doubled.

**Treatment of latent tuberculosis**

Regarding the treatment of latent tuberculosis: first of all, the drug of choice is isoniazid (300 mg/day supplemented with vitamin B6 for at least nine months. Some suggest prophylaxis for a year period. Alternatively, 2 months of rifampicin + pyrazamide or levofloxacin + ethambutol (6 months) may be used. On the other hand, prophylaxis is not devoid of side-effects; one always must consider the risk of hepatotoxicity, which may be seen in up to 37% of the patients.

Since tuberculosis is rare in many countries and since it is manageable, prophylaxis is not practiced widely. The best solution would be individualising the treatment of latent tuberculosis. Patients with initial or boosted tuberculosis skin testing with induration ≥5 mm or a positive IGRA, history of untreated latent tuberculosis, transplantation from a donor with untreated latent tuberculosis, and carrying a high risk for primary tuberculosis (e.g., recent history of contact with an individual with active disease) should be considered for prophylaxis (or treatment of latent infection).

**Conclusion**

Despite tuberculosis is a very old and well-known disease, and despite transplantation is being performed as the treatment of choice for end-stage renal disease for more than a half century, we still have many unknown variables for treating tuberculosis in transplant recipients. Collaboration with experts from many other fields is needed to offer the best management to our patients. Even more importantly, well-designed studies in transplant recipients with tuberculosis are strictly needed.

Mehmet Sukru Sever, Istanbul, Turkey

**S25: Infectious complications in transplant patients**

**Room: ELICUIUM 2**

**Date: 02–06–2014**

From 11:45 to 13:15
Current and future management strategies in a changing ADPKD landscape

Professor Albert Ong
Symposium Chair

Topics

Introduction – Evolution and new insights into the management of ADPKD
Prof Albert Ong (UK)

Clinical perspectives on assessing the natural progression of the disease
Prof Bertrand Knebelmann (France)

Current clinical management and new and emerging treatment options
Dr Andreas Serra (Switzerland)

Summary – A changing paradigm – what can we hope to achieve?
Prof Albert Ong (UK)

Lunch bags will be available at the start of the symposium.
Sponsored by Otsuka Pharmaceutical Europe Ltd.
Recent trends in dialysis care
International practices and improved outcomes: DOPPS

By observing patients over time, and correlating practices and outcomes in different medical settings around the world, the DOPPS helps researchers identify practices and other modifiable characteristics that improve patient lives. A symposium at the ERA-EDTA Congress gives insight into recent findings and developments.

EURODOPPS

The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a prospective cohort study of hemodialysis practices based on longitudinal data collected from a random sample of patients from a representative sample of hemodialysis units in each country. Launched in 1996, the DOPPS is currently ongoing in Belgium, France, Germany, Italy, Russia, Spain, Sweden, Turkey, the United Kingdom, as well as countries in North America, Asia, and the Middle East.

The DOPPS aims to identify modifiable practices associated with improved patient outcomes, including morbidity, mortality, and quality of life. The international scope of the DOPPS provides great variability in practice patterns and outcomes and enhanced ability to understand the relationships between various treatment effects and patient outcomes. The extensive DOPPS data set allows for detailed adjustment for potential confounders, thus limiting the possibility of biased findings.

Internationally, the DOPPS has served as a resource to monitor changes in hemodialysis practices as new clinical guidelines, regulatory changes, and treatment regimens are implemented. To maximise the potential impact on clinical practices, it is key that DOPPS collaborates with clinical investigators, scientists, and providers within each of the participating countries. In order to ensure that the DOPPS is fully used as a resource to maintain and improve the quality of dialysis care in Europe, the DOPPS has entered into a formal partnership with the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) called EURODOPPS.

Under the guidance of an oversight committee with representation from both organizations and European DOPPS country investigators, EURO-DOPPS data will be used to address scientific and policy questions that are of interest to the European nephrology community. To maximise efficiency and relevance to ERA-EDTA, DOPPS data collected in European countries (Germany, Italy, France, United Kingdom, Belgium, Spain, and Sweden) will be transferred to and analyzed by the ERA-EDTA Registry team.

Dr. Francesca Tentori, a DOPPS investigator, will present an overview of the new EURODOPPS partnership. DOPPS investigators and the ERA-EDTA leadership are excited to formally launch this collaboration and look forward to the many opportunities that the EURODOPPS initiative may open, with the final goal to provide evidence that will extend survival and improve the lives of hemodialysis patients.

CKDoppS: Improving outcomes in advanced CKD and the transition to dialysis

International differences between chronic kidney disease (CKD) prevalence and end stage renal disease (ESRD) incidence have been found, likely at least in part due to the effects of differences in CKD care on disease progression. The Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDoppS) is an international, prospective nephrology clinic-based cohort study to gain understanding of practice variation and identify practices associated with best outcomes for advanced CKD patients. CKDoppS launched in 2013/2014 in France, Germany, Brazil, and the US, where random samples of nephrology clinics and patients have been recruited to collect detailed data with up to 4 years of patient follow-up from >10,000 adult CKD patients from ~130 CKD clinics during the next 5 years. Among several study areas, one is to gather data regarding planning and preparation for the transition to end stage renal disease (ESRD) with follow-up for one year after the ESRD transition. Patient preferences and quality of life will be emphasised.

Dr. Benedicte Stengel, Principal Investigator for the CKD-REIN cohort study and a Country Investigator for CKDoppS in France, will provide an overview of the CKDoppS goals and design to identify practices associated with best outcomes for CKD patients and produce actionable findings relevant to patients, clinicians, policy makers, and other stakeholders. Preliminary data and characteristics of the study sample will be described. With local funding support, the inclusion of other countries in CKDoppS is encouraged and welcomed.

PDOPPS: Unifying efforts to improve outcomes in peritoneal dialysis

The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) is one of the largest prospective observational cohort studies among peritoneal dialysis (PD) patients to date. Modeled upon the success of the Dialysis Outcomes and Practice Patterns Study (DOPPS), and in collaboration with scientific input and leadership from the International Society for Peritoneal Dialysis (ISPD), PDOPPS is enrolling a representative sample of PD facilities and patients from Australia, Canada, Japan, the US, and the UK with several additional interested countries likely to join in the future. PDOPPS is designed to help understand the optimal practices that are associated with improved outcomes for PD patients, including extended technique survival, reduced mortality, and improved quality of life. PDOPPS is also providing a forum to promote effective collaborative international clinical research in PD as a vital means to strengthen the evidence base supporting PD treatment decisions.

Dr. Simon Davies, past President of the ISPD, will provide an update on the launch of the PDOPPS study and future directions. PDOPPS launched in Canada in October 2013 and in the United States in the first quarter of 2014. Japan, Australia, and the UK are poised to join by the middle of 2014.

Global trends in vascular access use, associated practices, and outcomes

The native arteriovenous fistula (AVF) is widely recognised as providing the best overall outcomes for hemodialysis (HD) patients and is the access of first choice for most HD patients compared with an arteriovenous graft (AVG) or central venous catheter (CVC). Catheter use has been associated with substantially higher rates of mortality, infectious complications, central venous stenosis, cost, and hospitalizations. Consequently, KDIGO and many national guideline committees recommend the AVF as the access of first choice for HD patients. Despite this, large variations are seen in AVF use across the 21 countries in DOPPS in 2012 and 2013, and with substantial increases in catheter use in some European countries during the last 10–12 years.

Dr. Michel Jadoul, a DOPPS country investigator, will discuss the many aspects of practice and processes of care related to vascular access (VA) use within a hemodialysis unit. This presentation will describe: 1) recent and longer term trends in VA use by country in prevalent and incident HD patients, 2) facility practices for monitoring achievement of access-related target levels and complications, 3) complication rates and temporal risk profile by VA type, 4) trends in VA procedure rates as efforts continue to extend long-term use of arteriovenous vascular access, and 5) use of buttonhole cannulation. The DOPPS has helped inform the worldwide HD community regarding key aspects of VA care and outcomes, and in this presentation will continue this focus upon providing evidence for vascular access practices associated with the best outcomes for HD patients.
A common cause of allograft failure

Human BK polyomavirus nephropathy

Human BK polyomavirus (BKV) nephropathy (BKN) remains one of the most common causes of renal allograft failure. The prevalence of BKN varies from 1% to 10%, and graft loss following onset of BKN ranges from 18% to 80%. Even though BKV was isolated already in 1971, the first nephropathy caused by it was diagnosed more than 20 years later. It was associated with the introduction of more potent immunosuppressive drugs including tacrolimus and MMF.

Donor kidney may be the source of BKV

Growing evidence shows that the donor kidney may be the source of BKV. Therefore, screening of the donor seems to be reasonable. To date, there is no effective therapy against BKV, the crucial approach is to prevent BKV in viruric or viremic patients. Viruria and viremia precede development of BKN.

Routine screening for BKV DNA by PCR in urine or blood with subsequent immunosuppression reduction during the first 2 years posttransplant is recommended. Persistent high viremia is associated with the greatest risk of BKN, however, a low viral load seems to not affect long term outcomes. The gold standard for the diagnosis of BKN remains renal biopsy with SV40 staining. Noninvasive prognostic factors which correlate with BKN were identified including urinary cell level of PAI-1 mRNA.

HLA antigens that are associated with a low predisposition to the development of BKN have also been identified. Management of BKV recently has been focusing on immune response to BKV. Innate immunity may have a pivotal role in BKN through activation defense mechanisms via TLR3. The development of BKV-specific T cells correlates with BK virus clearance and resolution of nephropathy, hence, immune monitoring may have a prognostic value. NK cells are an important component of the immune system in the control of viral infection. The roles of NK cells and KIR (killer cell immunoglobulin-like receptors) to eliminate the BK virus have been highlighted recently.

No established consensus on the treatment

There is no established consensus on the treatment of BKN. A reduction of the immunosuppression is crucial for clearance of the virus. Discontinuation of antiproliferative drugs, CNI dose reduction by 25-50% are the most common approaches. The potential of mTOR inhibitors to inhibit BKV replication and preserve protective immunity has been reported. Polyoma virus activates the protein Akt/mTOR pathway by triggering its replication and mTOR may inhibit this pathway. Data from clinical trials with everolimus showed a lower rate of BKV in patients receiving mTOR inhibitor when compared with patients on CNI or MMF. Conversion to mTOR is an attractive alternative to CNI reduction and de novo mTOR introduction in high risk patients is also suggested.

Reduction of immunosuppression is a risk factor for acute and especially chronic rejection. Renal function monitoring in 1 to 2 week intervals and DSA screening are recommended to provide a balance between the risk of BKN and the rejection risk. A meta-analysis of 40 studies did not show any graft survival benefit with addition of cidofovir or leflunomide. Cidofovir use is associated with nephrotoxicity and other serious side effects. Effective inhibition of BK replication by fluoroquinolones was recently reported. Ciprofloxacin has been suggested to interfere with helicase activity of BKV large T antigen. An anti-viral effect of ciprofloxacin was confirmed in several nonrandomized trials. Currently, a randomized clinical trial of ciprofloxacin for the prevention of BKV is being conducted.

Most studies showed that leflunomide therapy has not been associated with viral clearance however in the last pediatric study the use of stepwise approach with ciprofloxacin and leflunomide decreased the viral load and prevented BK in pediatric renal transplant recipients with minimal reduction of immunosuppression.

Retransplantation after allograft loss due to BKN is not a contraindications in case of negative BK viremia. Transplant nephrectomy is not necessary. Further research on screening, immune monitoring, treatment strategies of BKV is required.

Late breaking clinical trials II

Tomorrow the “Late breaking clinical trials” session will highlight these subjects: Jorge B. Cannata-Andia will discuss the “impact of parathyroidectomy and cinacalcet use on survival in chronic hemodialysis patients: the COSMOS study”. Colin Meyer shows some “investigation of serious adverse events in bardoxolone methyl patients in Beacon”. Charlotte Keyzer proves that “high serum calciumification propensity is associated with mortality and graft failure in renal transplant recipients”. Geoffrey Block deals with “a double-blind placebo controlled randomized trial of ferric citrate coordination complex for the treatment of iron-deficiency anemia and reduction of serum phosphate in patients with non-dialysis dependent chronic kidney disease.” Finally Joost Schanstra talks about “diagnosis and prediction for progression of chronic kidney disease by assessment of urinary petides.”

S 27: International Practices and Improved Dialysis Outcomes: DOPPS
Room: HALL 2
Date: 02-06-2014
From 15:15 to 16:45

S 25: Infectious complications in transplant patients
Room: ELICUIM 2
Date: 02-06-2014
From 11:45 to 13:15

S 18: Late Breaking Clinical Trials 2
Room: Hall 2
Date: 02-06-2014
From 8:00 to 9:30
Incidence much higher than previously thought?

Acute kidney injury in Europe: Some reflections on its epidemiology

Major global efforts have been made to study the basic and clinical aspects of acute kidney injury (AKI) over the last decades. In the framework of the symposium devoted to AKI in Europe and China during the ERA-EDTA congress of 2014, this letter briefly summarizes some contributions of European nephrology to the definitions and epidemiology of AKI as they have been evolved over the last decades. A recent systematic review of worldwide AKI studies revealed that from the total of 154 studies that used a KDIGO-equivalent AKI definition and were identified between 2004 and 2012, 51 studies (33%) originated from Europe, second only to the 70 studies originated from the Americas. However, a wide variety in the number of studies within the different European regions was noted.

Confronted with a wide array of definitions of AKI the recent development of several standardized classification systems and staging criteria for AKI have informed and advanced the epidemiology and natural history of AKI as well as its potential long term effects, including the development of progressive chronic kidney disease (CKD) and end-stage renal dis-ease (ESRD), and increased mortality risk. An important Austrian study by Lassnig et al. demonstrated already in 2004 that minimal changes in serum creatinine (Scr) were associated with increased mortality in patients developing AKI after cardiac surgery.

A major step forward was the formation of the Acute Dialysis Quality Initiative and the Acute Kidney Injury Network in both of which European investigators and clinicians were included. The most recent KDIGO guidelines define AKI by either an increase of Scr >0.3 mg/dL (>26.4 µmol/L) or an episode of oliguria (urine volume < 0.5 mL/kg/h for 6 hours) within 48-hours or an increase of Scr by >1.5-fold above baseline, known or assumed to have occurred within 7 days. One of the most discussed limitations in this definition is the importance of determining the baseline kidney function in patients admitted in AKI and in whom this baseline value is not known.

Whereas in general the KDIGO definitions have been accepted by the European nephrological community, the European Renal Best Practice expert group has amended these definitions by first specifically underlining that scoring and more extensively clarifying the need to use the first available (admission) serum creatinine in that episode as baseline creatinine instead of a retrograde calculation of this baseline value as suggested by KDIGO; and second by drawing attention to the fact that urinary volume should be expressed using ideal body weight rather than real body weight when calculating the urinary output in mL/min/kg. ERBP also felt that it was necessary to explicitly state that both criteria should be applied to classify patients.

Epidemiology of AKI in Europe

The incidence and outcome of AKI has varied according to population (ICU, non-ICU, and population-based), parameters used for the criteria (serum creatinine, GFR, and urine output), and timing of end-point (in-hospital mortality, 30 days, 60 days, or six months).

Critically ill patients: Some large European cohort studies on the epidemiology of AKI in ICU patients have been published. For example, the Riyadh Intensive Care Unit Program database of 41,972 patients admitted to 22 intensive care units in the United Kingdom and Germany between 1989 and 1999 revealed an incidence of AKI as defined by the RIFLE classification of 35.8% (15,019 patients; 7,207 (17.2%) patients were at risk, 4,613 (11%) had injury, and 3,199 (7.6%) had failure). The North East Italian Prospective Hospital Renal Outcome Survey on Acute Kidney Injury (NEPHROS-AKI), which was the first prospective, multicenter study, demonstrated the incidence of AKI in 19 ICUs in the three regions in north-eastern Italy during a three-month period. Of 2,164 ICU patients, 234 (10.8%) developed AKI, 19% were ‘risk’, 35% ‘injury’, and 46% ‘failure’. Overall mortality was highest among those in the ‘failure’ group (mortality: 20% ‘risk’, 29.3% ‘injury’, and 49.5% ‘failure’). The odds ratio for mortality based on RIFLE ‘failure’ criteria was significantly higher than the ‘risk’ criteria.

A recent national, multicenter, prospective, epidemiological survey evaluated the importance of AKI in 7 intensive care units (ICUs) in Hungary. In 459 patients admitted to ICUs between October 1st, 2009 and November 30th, 2009, 112 patients (24.4%) had AKI. By AKIN criteria 11.5% had Stage 1, 5.4% had Stage 2 and 7.4% had Stage 3. In 44.0% of patients, AKI was associated with septic shock.

The mortality of AKI patients who need RRT remains very high. For example, in a recent UK study of 821 patients who received RRT for AKI, the ICU mortality rate was 55% and the hospital mortality rate was 66%. Similarly, a Belgian study reported hospital mortality rates of 43% in patients with AKI who did not require RRT and 58% in those who did.

It is thus clear that in analogy with experience in other parts of the developed world, also in Europe the prognosis of patients with AKI remains poor, with ICU mortality rates of around 40%–60%. Moreover, despite considerable progress in renal sup-portive and replacement therapies, and some indication that survival rates may be improving, AKI is associated with prolonged length-of-stay and a higher incidence of end-stage renal disease. The economic consequences of AKI are considerable in terms of extended hospital stays and often prolonged, expensive therapies.

Community and hospital-acquired AKI: The incidence data on commu-nity and hospital-acquired AKI in Europe are relatively scarce and the information dates from before the new definitions have been introduced. As far known only two major population-based studies have been performed. Besides the classical study of Liano in Madrid, most other European studies in this field are coming from the UK/Scotland. Liano et al. found an incidence of AKI of 209 pmp/year in 1992 in Madrid (Spain) when AKI was defined by a sudden increase of Scr >177 µmol/L ( >2 mg/dl) or a sudden increase of 50% or more in patients with previous mild-to-moderate chronic renal failure (Scr <264 µmol/L or 3 mg/dl). In this study only hospitalised patients were included. Another study in Scotland during the same study period used a more specific definition for AKI (Scr >300µmol/L or 3.3 mg/dl) and included also non-hospitalised patients. In this study the incidence of AKI was 650 pmp/year. In 2003, the population incidence of AKI in the Grampian region of Scotland was 2,147 pmp/year – a figure lower than that reported in a study in a northern California cohort of Kaiser Permanente beneficiaries in the period 1996 to 2003. However, the incidence of AKI in the Scottish population was considerably higher than previously thought. Remarkably, the median age was 76 yr for AKI and 80.5 yr for acute on chronic renal failure patients. Sepsis was a precipitating factor in 47% of patients.

Even more disturbing is that a recent confidential survey in the UK showed that in 2009 only 50% of patients who died from a diagnosis of AKI received good care. Systematic failings in the recognition and management of AKI and its complications were found.

If all these studies could be con-sidered as representative for a general European population it is suggested that the incidence of AKI in Europe is much higher than previously thought, occurs mainly in the elderly segment of the population with implications for service planning and providing information to colleagues about methods to pre-vent deterioration of renal function. It is also clear that in Europe as well as elsewhere, it is necessary to improve the recognition and response to patients developing AKI and to improve the management of the condition once it has occurred.

In this regard, the introduction of a real-time alerting system of every worsening RIFLE class by the AKI "sniffer" in patients at risk for AKI may increase the number and timeliness of early therapeutic interventions with possible significant improvement of short- or long-term outcome.
A common disease and a great challenge

Acute Kidney Injury in China

Acute kidney injury (AKI) has been recognised as a major healthcare problem affecting millions of patients worldwide. It is strongly associated with the increase of resource utilisation, higher mortality, and higher risk for the development of chronic kidney disease (CKD). China is the largest developing country in the world. Since the definition of AKI was published by Acute Kidney Injury Network (AKIN) in 2005, it was widely adopted in clinical practice in China. Although the nationwide community based survey about the incidence and prevalence of AKI in China is still not available, a number of studies on specific groups of patients such as hospitalised patients, ICU patients or Children have been well performed.

Epidemiology

The incidence of AKI varies widely in China as elsewhere in the world, ranging from 1% to 44.3% due to the difference of studies (Figure1). In a prospective multicenter observational study performed by China Critical Care Clinical Trial Group (CCCTG), 3,063 consecutive patients from 1 July 2009 to 31 August 2009 in 22 ICUs across mainland China were enrolled. It was shown that 31.6% suffered from AKI, with aIFLE maximum class R, L, and F in 10.0%, 7.3%, and 14.3%, respectively. In another large retrospective cohort study based on hospitalised patients in Shanghai Zhongshan Hospital, 3,199 (5,619/176,155) admissions were diagnosed as AKI according to the AKIN criteria. Similarly, 2.41% (934/38734) of hospitalised patients were diagnosed with AKI in Shanghai Renji Hospital. It seems that the incidence of AKI in hospitalised patients in China is lower than that reported in USA. As to the distribution of AKI in hospitalised patients, 63.4% of AKI patients were found in surgical departments, 35.4% in internal medicine department, while the incidence of AKI in renal departments was only 4.5%. In another hospitalised investigation from the Coronary Care Unit in Nantong Hospital of Nanjing, 44.3% (445/1005) of acute decompensated heart failure patients developed AKI according to the RIFLE criteria, suggesting that this is a very high risk population for AKI and special care should be taken of these patients. To investigate the development of AKI in elderly patients, a consecutive series of 3,626 hospitalised patients with age ≥80 in Chinese PLA General Hospital was collected, they found the incidence of AKI (AKIN definition) was 14.8%.

Etiologies

Etiology study is also a key issue in AKI. Clinically, AKI could be attributable to the prerenal, intrinsic and postrenal diseases. The etiology of AKI also varies markedly depending on the origin of the database. In one single center study from emergency ICUs, the major causes of AKI were prerenal AKI (78.95%). The major causes of prerenal AKI were cardiovascular and cerebrovascular diseases. Another survey in hospitalised patients from Renji Hospital of Shanghai suggested that pre-renal AKI accounted for 52.08%, followed by renal parenchyma AKI (44.7%) and postrenal AKI (3.3%). The most common reason for AKI was acute tubular necrosis (37.9%), followed by absolute (33.6%) and relative inadequacy of blood volume (13.4%) in the hospitalised patients. On the other hand, infections, hypo-volemia, nephrotoxic drugs and cardiovascular diseases were the common causes for the very elderly hospitalised patients. Comparing to the adult etiologies, a large cohort paediatric patient study (388,736) demonstrated that the most common causes of paediatric AKI (diagnosed as according to AKIN criteria) were renal parenchyma diseases (57.52%), whereas postrenal (25.69%) and prerenal (14.96%) causes were relative less common.

It should be noted that drug-induced AKI is also very common in China. Based on an AKI registry originating from 17 hospitals in Shanghai, drug-induced AKI accounted for 28.9% of 1,200 cases. Antibiotics were the leading cause of drug-induced AKI (47.8%), followed by diuretics (22.2%) and radioccontrast agents (13.3%). In 2009, there was a sporadic epidemic AKI among children due to urorhismias which was linked to exposure to melamine-contamined milk. More recently, Chinese scientists have revealed that the potential mechanism for melamine-induced toxicity in rats might be related to the metabolic activities of the gut microbiota. Melamine induced a small amount of cyanuric acid generation through the gut microbial, which then leads to the development of melamine-cyanurate crystals in the kidneys.

Trauma is also one an important cause of AKI in China. The incidence of trauma-induced AKI in China is increasing in recent years with the industrialization of the country. On May 12, 2008, a devastating earthquake hit Wenchuan county of China’s Sichuan province. One study found that AKI occurred in 41.6% of crash syndrome (CS) patients (62/149) and 33 of them received renal replacement therapy. The overall mortality rate was 1.0% but mortality of patients with CS was 6.7% in the Wenchuan earthquake.

The new biomarker study for diagnosis of AKI is also an interesting subject in China. A meta-analysis collected 2979 patients from 11 eligible studies. Five prospective cohorts, two cross-sectional and four case-control studies were identified. The estimated sensitivity of urinary KIM-1 for the diagnosis of AKI was 74.0% (95% CI, 61.0%–84.0%), and specificity was 86.0% (95% CI, 74.0%–93.0%). Another meta-analysis from Nephrology Institute of Changzheng Hospital analyzed data from 23 studies involving 4,512 patients. They found the diagnostic odds ratio for urinary IL-18 level to predict AKI was 4.22 (95% CI, 2.90–6.14), with sensitivity and specificity of 58% and 75%, respectively. Though the availability of new biomarkers of kidney damage offers an unprecedented opportunity for improved evaluation and management of patients with AKI, the current evidence based biomarker study for AKI is limited, thereby restricting their clinical application.

Therapy

The treatment of AKI is still a challenging issue in China. Since most of the hospital acquired AKI is due to prerenal reason, early detection and prevention is paramountly important. Special care should be taken to the high risk patients to prevent hypo-renal perfusion, avoid nephrotoxic medications, and provide adequate fluid therapy. Renal replacement therapy including CRRT has been well established in the treatment of severe AKI patients in most of the urban hospitals in China. Our experience showed early CRRT had a significant clinical benefit to those with multiple organ disorder syndrome (MODS). There was a large cohort study retrospectively performed by Nanjing JinLing Hospital, analysed the outcome of 1692 critical patients. The continuous high volume hemofiltration and conti-nuous veno-venous hemofiltration were the main modal of CRRT. They found that 47.28% cases were cured and 27.07% were improved. Furthermore, CRRT could significantly reduce the mortality rate and provide better outcome for those with critical ill patients. In a prospective randomised clinical trial on 152 sepsis patients, Zhang et al demonstrated that high volume hemofiltration could provide a safe and efficient control of metabolic and fluid imbalance for AKI and MODS patients comparing to low volume hemofiltration. However, there is still quite controversial about the optimal initiating time and doses for CRRT in critically ill patients.

Conclusions

AKI is a common disease in China. Although many advances have been made in the past decade, there are still great challenges for Chinese nephrologists. We need to know the incidence and prevalence of AKI on the basis of national community survey. How to reduce the incidence of hospital acquired AKI is also an important issue. On the other hand, as the largest developing country in the world, our resources and facilities for saving the severe AKI patients is still limited for many remote regions. Obviously, the solution to these critical issues will not only rely on the technological progress and academic investment, the Chinese characteristic medical reforms is also eagerly expected.

Bi-Cheng Liu, Nanjing, China

S 31: Joint Symposium CSN & ERA-EDTA
Room: FORUM
Date: 02-06-2014
From 15:15 to 16:45
Klotho and ageing in CKD

Chronic kidney disease (CKD) is associated with an increased risk of death that is most dramatic in patients with chronic renal failure. CKD-associated organ damage shares features with physiological aging as well as with human syndromes of accelerated aging such as the Hutchinson–Gilford progeria syndrome, e.g. abnormal bone mineral metabolism leads to hyperphosphatemia, decreased renal excretion of phosphate, and vascular calcification. The description by Makoto Kuro-o et al. in 1997 of Klotho as the disrupted gene in mice with a specific form of accelerated aging shed light onto the potential relationship between the kidney and accelerated aging. Mice deficient in Klotho had features of aging that include osteoporosis, vascular calcification, hyperphosphatemia and early death. Klotho was found to be the earliest bone mineral metabolism-related factor to become abnormal during CKD.

One potentially important piece of the puzzle is the negative impact of inflammation and pro-inflammatory stimuli on Klotho expression by kidney cells. Klotho gene expression was found to be decreased in experimental acute kidney injury and the decrease in kidney Klotho could be prevented by therapy then targeting TWEAK, a pro-inflammatory cytokine of the TNF superfamily. Local kidney inflammation or systemic inflammation as a consequence of intraperitoneal administration of TWEAK resulted in decreased Klotho expression. More specifically, activation of the master transcription factor of inflammation NFκB decreased kidney Klotho.

Inflammation in distant organs impacts on kidney Klotho expression. Experimental gut inflammation leads to decreased kidney Klotho expression and this is prevented by neutralising anti-TNF antibodies. Additional pro-inflammatory stimuli, widely recognised as mediators of vascular injury also decreased Klotho expression in tubular cells.

Alberto Ortiz, Madrid, Spain
S 40: Mineral metabolism and clinical outcomes in CKD
Room: HALL 2
Date: 03-06-2014
From 10:45 to 12:15

High risk of end stage renal disease

Ethnicity is important for the response to treatment in patients with lupus nephritis

Lupus nephritis affects more than 60% of patients with systemic lupus erythematosus during their lifetime. Lupus nephritis belongs to the most serious complications of lupus with up to 15% of patients reaching finally end stage renal disease despite currently available treatment. Lupus nephritis (namely focal and diffuse proliferative lupus nephritis) also significantly shortens the patient survival. Renal damage may increase the risk of mortality in lupus patients by about 80% (Danila et al., 2009).

The outcome of patients with lupus nephritis significantly improved in the last 50 years due to the introduction of effective therapeutic protocols. However, only recently, effective, but relatively toxic initial treatment with the combination of corticosteroids and cyclophosphamide may be replaced by the combination of corticosteroids and mycophenolate mofetil. Mycophenolate favourably compares also with azathioprine in the maintenance treatment of lupus nephritis. Recent introduction of the targeted (biologic) treatment (rituximab, belimumab) may pave a completely new avenue in our approach to the patients with systemic lupus erythematosus and lupus nephritis, but we still need more data to better define the patients most benefitting from these newer modes of treatment.

Ethnicity is well known to play a role in the susceptibility to lupus (lupus may be more prevalent in African Americans compared to white population), but namely severity of different disease manifestations, in particular the risk of lupus nephritis, its response to treatment and long-term outcome. Recent studies suggested that the susceptibility to lupus in European and East Asian populations may be related to the admixture of Neandertal genes.

It is well known that lupus nephritis is compared to white patients more common among the African Americans, Hispanics and Asian patients. Recent study nicely demonstrated that the risk of developing lupus nephritis is decreased in patients with systemic lupus erythematosus in relation to the degree of their European ancestry (Richman et al., 2012). Although in the last decade there were many genetic studies in patients with systemic lupus erythematosus the genetic reasons for this difference still remain to be better elucidated.

Outcome and response to treatment is also different in patients with different ethnicity. It is well known that African American and Hispanic patients have poorer outcome and poorer response to treatment compared to white patients and may have also more adverse events of treatment. It is, however, necessary to stress that poorer outcome of African-Americans and Hispanic patients may also be influenced by other factors except for the ethnicity, e.g. poverty, lower socioeconomic status and lower education resulting in delayed diagnosis and uneven access to the good quality health care (Barr et al., 2003) and also by higher prevalence of hypertension and diabetes. Genetic factors are, however, believed to play a more important role than socioeconomic status and a substantial part (about 40%) of the ethnicity-related difference in the risk of developing lupus nephritis in systemic lupus erythematosus and the outcome of lupus nephritis remains unexplained (Borchers et al., 2010).

It is well known that European (white) patients with lupus nephritis compared to African Americans or Hispanics respond much better to the treatment with cyclophosphamide. EUROPUS trial (and the data from its long-term follow-up) unequivocally demonstrated that in European (mostly white) patients lower doses of cyclophosphamide induce remission of lupus nephritis as effectively as higher doses necessary to treat the same disease in African-Americans.

In the recent multiethnic ALMS trial mycophenolate was in white (and Asians) patients similarly effective as cyclophosphamide as induction treatment of lupus nephritis whereas in other patients (including African Americans) mycophenolate was more effective namely because the lower efficacy of cyclophosphamide in black, Hispanic and Latin Americans patients (Isenberg et al., 2010). On the other hand, serious adverse events were more common in mycophenolate-treated Asian patients.

Similarly, mycophenolate was more effective as a maintenance treatment of lupus nephritis in the multiethnic population of the ALMS trial (Dooley et al., 2011), but was similarly effective as mycophenolate mofetil in the mostly Caucasian population of the MAINTAIN trial (Housiau et al., 2010).

Retrospective analysis suggests that in Hispanic and black patients there may be also worse response to B-cell depleting drug rituximab (Ramos-Casals et al., 2011). High proportion of black and Hispanic patients may have also contributed to the absence of significant positive effect of add-on rituximab in the only randomised controlled trial in lupus nephritis, the LUNAR trial (Rovin et al., 2012). Large trials (BLISS-52 and BLISS-76) with the inhibitor of B-cell stimulating factor (Blys/BAFF) mixed together a multiethnic population of Caucasians, Hispanic, African American and Asian patients and the subanalysis of the efficacy and safety based on the ethnicity has not yet been published (Kandala et al., 2013). A randomized controlled study testing the efficacy of belimumab specifically in black adults with systemic lupus erythematosus is currently underway.

Conclusion

Systemic lupus erythematosus may be less prevalent in European white population and the risk of lupus nephritis is lower in patients with European ancestry. Lupus nephritis confers the patient not only with the risk of developing end stage renal disease, but also significantly shortens their survival. Lupus nephritis in European patients responds better to cyclophosphamide compared to African Americans and Hispanic patients and remission may be induced by lower doses of cyclophosphamide. European patients with lupus nephritis may even respond better to the biologic treatment with rituximab, but different response of European patients to rituximab and possibly also to other biologic treatments is only to be clearly demonstrated.

Vladimir Tesar, Prague, Czech Republic
S 31: Joint Symposium CSN & ERA-EDTA
Room: FORUM
Date: 02-06-2014
From 15:15 to 1:45
INTRODUCING 360° OF HIGH DOSE HD INNOVATION

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Adressing the underutilisation of PD in Europe

Although long-term morbidity and mortality are comparable between PD and HD, there is an early patient survival advantage for home-based PD. Moreover PD can be an effective treatment for a wide range of patients from children to the elderly and in many countries is a more cost effective therapy compared to conventional hospital-based HD. Nevertheless, only one out of 10 patients on dialysis is treated with PD in Western Europe although there is considerable variation between countries – under 5% in Germany and approximately 30% in some Nordic countries. In addition a higher percentage of patients receive PD in other parts of the world e.g. Mexico, Australia and Hong Kong. This suggests that there is a general underutilisation of PD in Europe and that this is due to non-scientific factors such as the lack of clinical PD experience, knowledge and confidence from nephrologists. A further limitation to PD remains the repeated exposure to the patient with PD fluids (PDFs) containing high glucose concentrations. There can be toxic and inflammatory insults to the cells of the peritoneum that lead to both peritoneal membrane damage and potentially local infection due to inhibition of peritoneal host defenses.

Early identification of PD patients at risk of peritoneal membrane damage by identifying new biomarkers, may allow individually tailored, specific, novel therapeutic inventions in order to increase technique survival with PD. There are many opportunities for improvement in PD therapy. Understanding the addition of anti-inflammatory agents, which may prevent damage, may improve clinical outcomes. Knowledge of 5 biomarkers that allow the prediction of outcome in PD and 3 therapeutic treatments to improve outcome in PD. Both the treatments and biomarkers will have specific targets, be rigorously tested in lab based experiments and will be checked with clinical data from existing databases. The 12 partners in EuTRiPD include academic and industrial partners and the collaboration between them will ensure these results are maximised to their full potential by planning large multi-centre clinical trials for testing of these new therapeutic and diagnostic tools. The academic partners expect improvements in healthcare in their respective clinical practice, increased knowledge and visibility of their expertise through publications and training experience. In addition, through the EuTRiPD outreach programmes the partners interact with patient organisations, research organisations and governments to ensure there is wider knowledge of the impact of end stage kidney failure and the role of PD.

Goals and Objectives

European Training and Research in Peritoneal Dialysis (EuTRiPD) is an EU funded training programme which is funded for 3 years to train young researchers in a collaborative framework with experienced PD focused principal investigators. EuTRiPD aims to address the issue of underutilisation of PD by training young multidisciplinary researchers who are specifically qualified to understand and work within and beyond all the disciplines, sectors and audiences of PD. This will facilitate improvements in PD outcomes by developing future specific therapies in populations with a high risk of complication. The specific scientific aim of the programme is to develop a miniaturized, long-lasting and intersecto-

Content and structure of the EuTRiPD training programme

EuTRiPD supports the training of twelve Early Stage Researchers (ESRs) that primarily consists of Training Through Research within their individual projects carried out mainly at the host institution, but also taking advantage of the knowledge and expertise of other network partners through secondments. This leads to a broad training programme that includes core clinical knowledge and state-of-the-art PD research exposure as well as commercial experience and public awareness. This programme has a clear emphasis on providing translational training that integrates these different aspects and exposure to academic as well as private and public sector partners.

As well as their individual projects the ESRs attend biannual EuTRiPD academy. These academies last of 3-5 days and include intensive lectures, workshops and networking covering a wide variety of areas in PD research. These areas are not limited to purely research topics but also cover socio-economic, patient care, and private sector interests. In addition, the ESRs attend Associate Training Modules provided by partners of EuTRiPD: Kidney Research UK, The Dutch Kidney Foundation and EuroPD. As part of their specific training, ESRs will attend local training courses at the institution in which they are working. ESRs will also undertake short term stays with EuroPD partners to provide a broad knowledge of industry and academic work.

Furthermore complementary skills, like entrepreneurship, international networking communication skills, assessing patient needs are taught in order to broaden the experience of ESRs and enhance their own networking and collaborative abilities.

Structure of EuTRiPD research collaboration

EuTRiPD research is structured (Fig 1) into three work packages (WP), each using a multitude of different techniques to work towards finding biomarkers and therapeutic interventions. WP1 focuses on investigating cellular workings and the relationships between cell types relative to PD by looking at the cell signalling pathways. WP2 centres on in vivo modelling of the inflammation mechanisms in cutting edge rat and mouse models. WP3 targets the Biobanks (clinical databases and biological samples) from PD patients in order to examine outcome data related to targets identified in WP1 and WP2.

It is EuTRiPD’s belief and mission to supply Europe with young, well trained professionals in renal research and PD with excellent inter-sectoral career options in the general medical research field, in order to improve patient outcomes and to address the general underutilisation of PD in Europe. EuTRiPD will continue to make a committed contribution to boost currently hampered diagnostic and therapeutic developments in RRT in a unique long-lasting combined effort to structure existing high quality public and private PD related research across Europe. The impact of EuTRiPD on social (better quality of life of patients), economic (moneysaving) and scientific aspects (coordinated, long-lasting and intersectoral research and training) therefore can and will be enormous.

Evelina Ferrantelli, Marc Vila, Georgios Liappas, Anna Machovska, Tanja van Wier – van der Schaaf and Robert H.J. Beelen, Amsterdam, The Netherlands

S32: Different perspectives of peritoneal dialysis

Room: HALL 2
Date: 02-06-2014
From 17:00 to 18:30
New Artis Physio™ system
Achieve your treatment goals consistently

**Diascan™ monitoring system**
Facilitates delivery of the prescribed dialysis dose¹

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Predictable and efficient sessions through reduction of IDH²

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References
New potential therapeutic targets

Micro-RNAs on Immunoglobulin A1 glycosylation in IgA Nephropathy

IgA1 is largely predominant. High serum levels in 35-50% of patients. The IgA1 class is associated with recurrent episodes of glomerulonephritis. We recently studied the miRNA expression profile of peripheral blood mononuclear cells in IgAN patients (1). We identified a miRNA classifier represented by 35 upregulated and 2 downregulated miRNAs. We validated six of them as miR-148b, miR-188-5p, miR-361-3p, miR-886-3p, let-7b and let-7d. In silico analysis of miRNA targets (bioinformatic analysis) predicted some target genes like C1GALT1 for miR-148b and GALNT2 for let-7b. Other putative target genes of miR-148b are inversin (INVS) and phosphate and tensin homologue (PTEN), two genes that we found downregulated in patients with IgAN (2). The Ingenuity Pathway Analysis (IPA) software demonstrated that miRNAs were strongly interconnected with miRNA network. In particular, let-7d directly regulated PTEN, miR-361 regulated INVS, miR-148b regulated INVS and PTEN, and 3 miRNAs (let-7d, let-7a and miR-90) indirectly regulated AKT through RET.

Since C1GALT1 is known to be directly involved in IgAN, we evaluated C1GALT1 mRNA expression levels and we found that these levels were significantly lower in patients with IgAN. The in silico analysis demonstrated that the miR-148b increase could be directly involved in IgAN because the modulation of the C1GALT1 protein expression was also controlled by miR-148b. Finally, we validated the relationship between miR-148b expression and altered IgA1 glycosylation measuring miR-148b expression levels by real-time PCR and serum levels of Gal-deficient IgA1 in a cohort of IgAN patients and healthy subjects. Our results demonstrated a positive correlation between the upregulated expression of miR-148b and high serum levels of deglycosylated IgA1.

Recently, we used the same study approach for let-7b and we demonstrated that there was a positive correlation between high expression of let-7b in PBMCs of IgAN patients and low serum levels of deglycosylated IgA1. Let-7b is encoded by the relative gene located in the chromosome 22q13.31. We used four different algorithms in our bioinformatic analysis to predict potential let-7b target genes and we found that the GALNT2 gene is one of the potential targets.

On the basis of these results we can hypothesize that 1) there is a synergetic mechanism between let-7b and miR-148b in the regulation of IgA1 O-glycosylation process because we observed a direct correlation between these two miRNAs. In fact, IgAN patients with high expression of let-7b have high values of miR-148b; 2) in IgAN patient the low activity of two enzymes C1GALT1 and GALNT2, is due to the inhibiting effect of overexpressed miR-148b and let-7b as shown by our ex vivo transfection experiments. This abnormality leads to an increase of circulating serum deglycosylated IgA1 that are predisposed to the aggregation and formation of polymeric IgA1. The abnormally glycosylated IgA1 is considered as non-self by the immune system and induces the production of IgA1 antibodies like IgG thus forming IgA1-IgG immune complexes. The prolonged deposition of polymeric IgA1 and/or IgA1-IgG immune complexes is responsible for mesangial cell proliferation, overproduction of extracellular matrix and synthesis of inflammatory cytokines that can initiate and perpetuate the renal damage in IgAN (see Figure 2).

In conclusion, we have today two new potential therapeutic targets in IgAN because the modulation of these two overexpressed miRNAs (miR-148b and let-7b) may reverse the low levels of C1GALT1 and GALNT2, indirectly reducing the deposition of IgA1-IgG immune complexes at glomerular level.

Continued on page 21
A new view on adipocyte pathophysiology

Adipose tissue cytokines network in progressive renal diseases: clinical and experimental insights

During the last two decades results of both experimental and clinical studies have changed our view about adipocyte pathophysiology.

Since leptin was discovered in 1994, white adipose tissue has been recognised as an endocrine organ and an important source of biologically active substances with local and/or systemic action called adipokines. Inappropriate secretion of several adipokines by the excessive amount of white adipose tissue seems to participate in the pathogenesis of obesity-related pathological processes including endothelial dysfunction, inflammation, atherosclerosis, diabetes mellitus and chronic kidney disease.

The two major and well described adipokines are leptin and adiponectin. Leptin plays a role in appetite regulation and energy expenditure. However, in obese subjects leptin may participate in the pathogenesis of hypertension and chronic kidney disease. In contrast to leptin, adiponectin secretion is decreased in obese subjects. Adiponectin exerts a beneficial effect on the cardiovascular system and kidney function. Inappropriate low plasma adiponectin concentration is observed in patients with arterial hypertension, atherosclerosis, metabolic syndrome and diabetic nephropathy. In obesity, reduced adiponectin levels are associated with insulin resistance, cardiovascular disease and obesity related kidney disease. The latter includes microalbuminuria, glomerulomegaly, overt proteinuria and focal segmental glomerulosclerosis.

Adiponectin levels in type 2 diabetes also negatively correlate with early features of nephropathy. The mechanism of the action of adiponectin in the kidney appears to be related to AMPK activation and NADPH oxidase while low adiponectin levels may cause podocyte dysfunction (Figure 1). It seems that inadequate low plasma adiponectin concentration may play an important role in cardiovascular complications in patients with chronic kidney disease. Increased plasma concentration of resistin and visfatin was also related to a higher mortality rate in patients with chronic kidney disease. It is important to stress that all components of the renin-angiotensin system are produced by adipocytes. Locally secreted angiotensin II may play an important role in the pathogenesis of hypertension and vascular remodeling. Finally, adipocytes may secrete an aldosterone releasing factor which may directly stimulate aldosterone production by the adrenal glands. Hyperaldosteronism found frequently in obese subjects may participate in the pathogenesis of chronic kidney disease progression and the cardiovascular complications observed in these patients. Conclusion: Adipose tissue plays an important role as an endocrine organ and adipokines participate in chronic kidney disease progression and cardiovascular complications in these patients.

Andrzej Wiecek, Katowice, Poland

$ S 20: Overweight and obesity as dominant drivers of the CKD epidemic
Room: ELICIUM 1
Date: 02-06-2014
From 8:00 to 9:30

Continued from page 20

Abnormal formation of deglycosylated IgA1.

MiRNAs are a family of small, non-coding RNAs that control gene expression by inhibiting the translation of their complementary ‘target’ messenger RNAs (mRNAs). They can facilitate the degradation of mRNA target or inhibit its protein translation. Deregulated miRNA expression has been identified in human diseases and potential modulation can attenuate their effects. Several approaches can be used for ablating or overexpressing miRNAs for therapeutic applications. First, the use of antisense oligonucleotide inhibitors (antagonostars) that can be produced chemically. They target mature miRNAs. Second, the use of miRNA sponges that are genetically engineered for becoming competitive miRNA inhibitors. Third, the introduction of oligonucleotides that may interfere with the binding of the miRNA as masking or target occupation. Fourth, the use of eraser which is a tandem repeat of a perfect complementary sequence of the target endogenous miRNA.

These strategies have been used with great success in animal models; however, it is necessary to take into consideration that manipulation of miRNAs may involve many pathways in a disease. In our case miR-148b and let-7b, upregulated in IgAN patients, downregulated the target genes, C1GALT1 and GALNT2, respectively, causing aberrant glycosylation of IgA1. In addition, upregulated miR-148b downregulates INVS and PTEN genes causing proliferation of lymphocytes and mesangial cells. We suggest that by modulating the activity of both deregulated miRNAs (miR-148b and let-7b) it is possible to better control the abnormal glycosylation process of IgA1 occurring in IgAN patients, and the progression of renal damage caused by the hyperactivity of Wnt and PTEN pathways. The question arising from this suggestion is “Are there drugs, currently used in the clinical practice, available for modulating these upregulated miRNAs?” Recently, fribates as ligands for PPARα have been considered drug targets for regulating miR-21 involved in renal fibrosis. We are studying some molecules as modulators of miR-148b and let-7b.

Francesco Paolo Schena, Bari, Italy

$ S 30: Micro-RNA: a new biology frontier in kidney diseases
Room: EUCLiUM 1
Date: 02-06-2014
From 15:15 to 16:45

References
Thrombotic microangiopathies (TMAs) are a group of conditions characterised by endothelial injury that results in intravascular thrombi in small vessels with resultant microangiopathic haemolytic anaemia. Shiga toxin associated Haemolytic Uraemic Syndrome (Stx-HUS) and atypical HUS (aHUS) are TMAs with a predominant renal phenotype.

While the outcome of patients with Stx-HUS is good with most patients regaining renal function, the outcome of aHUS was historically poor with most patients dying or reaching end-stage renal failure.

Genetic studies into aHUS revealed the role of complement in the pathogenesis of disease. Inherited loss of function defects in the complement regulatory proteins, CFH, CFI, CD46 and gain of function mutations in the complement components C3 and CFB pointed to complement over activation in aHUS. Those with CD46 mutations tend to have a better outcome than those with mutations in the plasma complement components. In addition to predicting the outcome in native kidneys, genotype phenotype correlations are also seen following renal transplantation. Those with mutations in the membrane bound CD46 have a better outcome than those with mutations in plasma factors.

This understanding of the importance of complement over activation in aHUS led to the successful trial of the complement inhibitor, Eculizumab in disease. Eculizumab is now considered the gold standard for management of aHUS.

Despite its widespread use in the German Escherichia coli 0104:H4 outbreak the role of Eculizumab in Stx-HUS is less clear. As with many infections, the complement system can be seen to be activated in Stx-E. Coli infections, however, it is unclear if this is directly responsible for Stx-HUS. The normally self limiting nature of Stx-HUS means that a randomised controlled trial is required to establish the efficacy of Eculizumab in this setting.

David Kavanagh, Newcastle upon Tyne, UK

S 34: Genetics: monogenetic diseases
Room: ELICUIUM 2
Date: 02-06-2014
From 17:00 to 18:30

Complement activation in aHUS: The complement system through the Alternative Pathway is in a state of continuous low level activation with generation of a fluid phase C3 convertase (C3bBb). This generates the active form of C3, C3b, that can bind to cell membranes which leads to cell bound C3 convertase. If unchecked this process leads to rapid amplification of complement activation and generation of the effector proteins of the system; C5b-9, C3a, C5a and more C3b. To prevent this there are cell surface (MCP) and fluid phase (CFH and CFI) inhibitors of complement activation. Failure to adequately control activation leads to endothelial injury, with thrombus formation, red cell fragmentation and platelet consumption.

Complement Regulation

Complement Activation

Cell Lysis
Membrane Attack Complex (C5b-9)

Inflammation
Anaphylatoxins (C3a, C5a)

Opsonization (C3b)

Alternative Pathway

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New insights and developments in EPS

Risk of encapsulating peritoneal sclerosis should not discourage from starting PD

Encapsulating peritoneal sclerosis (EPS) is a severe complication of long-term peritoneal dialysis (PD) with a 50% mortality rate. EPS is characterised by progressive and excessive fibrotic thickening of the peritoneum, leading to encapsulation of the bowels and intestinal obstruction. The prevalence of EPS is low but the severity of the condition has a negative impact on the choice for PD as renal replacement therapy.

Traditionally, the pathophysiology of EPS is described as a multiple-hit process with a central role for transforming growth factor β, a profibrogenic cytokine which at least in animal models is pivotal for the development of peritoneal sclerosis. In PD patients the continuous exposure of the peritoneal membrane to dialysis fluids leads to a low-grade chronic inflammatory response to unphysiological circumstances, eventually leading to a mild degree of sclerosis. This inflammatory-sclerotic response is usually rather benign and may not cause any problems even after years of PD. However, in some patients the prolonged exposure to PD fluids does set the stage for increased peritoneal inflammation and excessive sclerosis, resulting in the clinical entity of EPS. With or without immunosuppressive medication, the peritoneal inflammation will eventually subside leaving behind a sclerotic cocoon of acellular scar tissue. The current data show that time on PD is the single most important factor associated with the development of EPS. Development of EPS in the first 3 years is rarely seen but thereafter the incidence exponentially increases with years on PD and may be >10% after 8 years. Younger age and a higher peritonitis incidence have been identified as additional risk factors.

Classical / post transplantation EPS

In 2007 we reported about an increasing incidence of EPS in former PD patients after kidney transplantation. This specific condition was coined post-transplantation EPS, as opposed to classical EPS occurring in patients on PD or switched from PD to hemodialysis. Post-transplantation EPS reportedly has a prevalence of 1-3% and the mortality is less compared to classical EPS. However, it contributes significantly to overall mortality in otherwise uncomplicated, relatively young patients with a functioning kidney transplant.

Recently, we were able to show that PD patients that will develop EPS already have a slight but significantly increased serum C-reactive protein concentration compared to a matched PD patient control population (Figure). In classical EPS patients, a complicated peritonitis episode was frequently observed within 6 months before clinically overt EPS. These observations are of considerable interest as they show that before the diagnosis of EPS there is an increased inflammation of the peritoneal membrane. The use of a profibrotic calcineurin inhibitor after transplantation or the accumulation of intra-peritoneal profibrotic factors after cessation of PD may both play a role. In classical EPS, peritonitis seems to be, relatively frequent, an important second hit for the development of EPS.

Can we predict EPS?

There is an ongoing search for biomarkers and functional tests that can predict which PD patients are at risk for developing EPS after prolonged PD treatment. It has become clear that progressive loss of ultrafiltration capacity is specifically associated with an increased risk for EPS. In addition, patients with increasing evidence of loss of mesothelial cell mass as indicated by decreasing effluent CA-125 concentration or increased intra-peritoneal production of interleukin-6 (a profibrogenic cytokine) are at risk for EPS. Recently it was shown that effluent PAI-1 (plasminogen activator inhibitor) concentrations are progressively increasing in the peritoneal dialysate, several years before EPS is diagnosed. Again these data show that EPS does not occur out of the blue. Patients with increasing inflammation, damage and sclerosis of the peritoneal membrane after several years of PD are prone to develop EPS.

How to diagnose EPS?

Signs and symptoms of bowel obstruction in combination with specific findings on abdominal CT scanning are the cornerstones of establishing the diagnosis of EPS. In advanced cases of EPS, the diagnosis is usually straightforward with ascites, bowel obstruction and retracted intestines encased by a thick sclerotic membrane. The diagnostic CT criteria for EPS have now been described but it is clear that regular CT scanning cannot identify patients at risk for EPS. Also, some patients have a relatively thin sclerotic membrane, which encapsulates the intestines but cannot be recognised by CT scanning. Other patients have a more localised EPS, with a predilection for the terminal ileum region, which also can be difficult to recognise by imaging techniques of the abdomen. Therefore, we advocate that exploratory surgery is mandatory in former PD patients with complaints of bowel obstruction without a satisfactory explanation, in order to exclude EPS as the cause. The histology of the sclerotic membrane is unique but is of little aid in establishing the diagnosis.

Novel treatment strategies

Based on the inflammatory nature of EPS, several anti-inflammatory drugs have been used. In particular, the use of high dose steroids and tamoxifen is now advocated, although direct evidence for their efficacy is lacking. However, there are some striking similarities of EPS with idiopathic retroperitoneal fibrosis, a condition for which both steroids and tamoxifen are of proven benefit. In particular, tamoxifen is an interesting drug as it has few side effects and its use was associated with less mortality in EPS patients. When the inflammatory phase has subsided the remaining sclerotic cocoon may still cause bowel obstruction. In these situations, surgical intervention may be the best option to avoid problems associated with parenteral feeding. EPS specific surgery, usually consisting of both peritonectomy and enterolysis, has been en vogue in Japan for some decades. Only in recent years dedicated EPS surgical centres have opened in Manchester, Cambridge and Stuttgart. In these experienced and dedicated surgical centers, post-operative mortality and morbidity is acceptable. This is a major improvement in the care for these patients who used to have a very poor prognosis. In the Netherlands we have established the Dutch EPS registry in 2009, which was extended to a European EPS registry in 2011. The insights gained from this registry have led to a published algorithm for diagnosing and treatment of EPS.

Future perspectives

The renewed interest for EPS has led to better understanding of the pathogenesis and improved diagnostic criteria. In addition, the treatment options are now better identified and specifically EPS dedicated surgical centers have made a real difference in the formerly bleak prognosis of severe cases of EPS. In Japan, the incidence of EPS has declined by the nationwide introduction of biocompatible PD fluids, and an active policy to consider discontinuation of PD treatment in patients with ultrafiltration failure and long duration of PD treatment. In general, the risk of EPS should not discourage doctors and patients from starting PD or discontinue PD after a number of years. However, there still is a real need for further clinical research to identify the early stages of EPS in asymptomatic patients, to clarify additional risk factors for EPS and to define optimal treatment strategies.

Michael Betjes, Rotterdam, The Netherlands

ISSUE 2 / June 1, 2014
Unmasking salt sensitivity in man
Concept and perspectives of the Salt Blood Test

Traditional foods (e.g., bread, cheese, sausages, sauces, ready meals, etc) often contain high amounts of salt (sodium chloride) that promote premature aging of blood vessels. Vascular endothelium is particularly sensitive to high sodium losing its protective negative surface charges by excessive amounts of salt. Erythrocytes circulating in the bloodstream 'grind' along these surfaces and thus get gradually damaged. A recently developed blood test quantifies this process and, at the same time, allows insight into the status of blood vessels. The test detects the vascular sensitivity to salt which could significantly increase the motivation for meaningful prevention.

Over millions of years, man ingested about 1 gram of salt (NaCl) per day. Recently, some 8,000 years ago, humans increased their daily salt consumption tenfold. This came along with salt-preservation of food stuff allowing former nomads to settle. From the physiological point of view, however, the kidneys are frequently overwhelmed in their excretion capacity. As a consequence, sodium is deposited in the extracellular space of the body and thereby damages the organism in long term. One of the first ‘anchor sites’ for ingested sodium is provided by the negatively charged surface film of the inner vessel wall, the endothelial glyocalyx. This protective layer is damaged by high salt concentrations rendering the organism vulnerable transit zone for merciless sodium-fingers on the surface of erythrocytes. The consequences of this endothelial dysfunction become apparent only when clinical symptoms occur. Then, however, the vascular system could be already severely affected. Therefore, also from an economic point of view, it is of great importance that salt sensitivity should be diagnosed at an early stage.

Erythrocytes 'mirror' vascular endothelium

The so-called Salt Blood Test (SBT) is based on the above described concept [2]. It is based on the observation that the surface of erythrocytes buffers sodium. As more negative charges are available as better is its sodium buffer capacity. Since the latter reflects the quality of the vessel wall, it is possible to indirectly determine salt sensitivity of blood vessels simply from a blood sample. Only a small amount of washed erythrocytes suspended in two electrolyte solutions composed of different sodium concentrations is necessary. Erythrocytes with high sodium buffer capacity (high density of negative surface charges) adhere less strongly to each other and thus travel more slowly than those with low sodium buffer capacity (figure 1). The procedure is technically simple, requires only about a milliliter of blood, two sodium containing solutions, standard glass tubes and a simple table-top centrifuge. The whole procedure takes about 60 minutes (from start to result). It allows quantifying the salt sensitivity of an individual and assessing its vascular state (figure 2). Background and concept of the salt test is reviewed in [3].

Perspectives of the SBT in hemodialysis

In chronic kidney disease (CKD) patients the inner wall of blood vessels is often damaged resulting in abnormal sodium binding capacity at the surface of the erythrocytes. This can be quantified by the SBT. Furthermore, the SBT could be used before and after hemodialysis in order to find out to what extent erythrocytes ‘suffer’ when passing through the hemodialysis tubings multiple times. Since the negative charges of both the erythrocyte and the endothelial surfaces physiologically prevent adverse mechanical interactions between the respective surfaces, ‘intelligent’ tubings (e.g., charge coating of the tubings) could help to preserve or even improve erythrocyte function during ongoing hemodialysis.

References:
Potential to become a mainstay

The role of tolvaptan in the treatment of polycystic kidney disease

Polycystic kidney disease (PKD) is an important disorder. At a reported prevalence of 0.1 to 0.4 % in Caucasians the number of PKD patients in the European Union is between 500,000 and 2.2 million. PKD causes substantial morbidity and mortality. Eighty to ninety percent of PKD patients will require renal replacement therapy by the age of 70. At present, there are no disease modifying therapies available. Obviously then efficient treatment for PKD would be extremely useful.

Twenty-five years ago the laboratory of Dr. Jared Grantham, Kansas City, Kansas was the first to study renal cysts in renal epithelial cell models. As they discovered an enhanced generation of the intracellular second messenger cAMP was characteristic and instrumental to cyst formation. Increased cAMP augmented proliferation of epithelial cells in the walls of cysts and it stimulated transport of chloride (and water) into the cyst lumen. The authors proposed that a combination of proliferation and secretion would make renal cysts grow. They concluded that the latter was eventually responsible for the loss of renal function.

The role of polycystin-1

In 1993 Breuning et al. described the gene for polycystin-1 which causes polycystic kidney disease type I when it is mutated. One function of polycystin-1 is that of a cell membrane calcium transporter, permitting calcium to be translocated from the extracellular to the intracellular milieu. Mutations of polycystin-1 impair its normal function(s). As a result intracellular free ionized calcium concentrations are diminished, phosphodiesterase activity falls and cAMP levels rise. Hence the consequences of the predicted molecular changes in PKD appear(ed) to be in agreement with the concept of an increased cAMP derived from renal cell models of cyst formation.

Most of the renal cysts in PKD originate from collecting duct epithelia (CD). Under normal circumstances the collecting duct handles water reabsorption. This function is mediated by antidiuretic hormone, the renal V-2 vasopressin receptor and cellular cAMP. In other words cAMP in CD cells is normally influenced and controlled by vasopressin. It may be hypothesised that the same applies to CD derived cysts as well. Conceivably then vasopressin-antagonist medications could be candidate interventions to lower cAMP in renal cystic epithelia. As a consequence the course of PKD may be modified, potentially improved.

**Mozavaptan reduced formation of renal cysts in a rat model**

A rationale of this kind has been tested in several animal experiments. In a PKD model termed the ‘PCk rat’ it was observed that the vasopressin antagonist mozavaptan lowered renal tissue cAMP, reduced the formation of renal cysts, kept kidney size normal, was associated with a lower blood urea nitrogen and prevented the increase of arterial blood pressure that occurred in untreated PCk rat. Comparable observations were also made in a PKD model termed the ‘pcy mouse’. Other PKD models and different vasopressin antagonists yielded similar results. Animal experiments thus supported the view that vasopressin antagonists can be effective in the treatment of PKD. It was concluded that this may apply to patients with PKD as well. (To be sure research avenues other than influencing cAMP in PKD have been pursued, too.

To mention only a few from that area: there have been experiments with the calcium channel stimulator tropolide; with chloride channel inhibition by CFTR inhibitors; with antiproliferative action by mTOR inhibitors; with antiproliferative effect by cdk inhibitor R-Roscovitine; with downregulation of TSC-beta catenin pathway by the PPAR-gamma agonist pioglitazone; with transcriptional upregulation by Trichostatin-A and a number of other approaches.)

The preclinical investigations mentioned led to a small phase II exploratory study – termed Tempos 2/4 – in 63 patients in 2004 (E Higashihara et al., Clin J Am Soc Nephrol 2011:6:2499-2507). In it participants took 60 to 90 mg/day orally of the V-2 vasopressin antagonist tolvaptan for 3 years. Their diagnosis of ADPKD-I was established according to the modified Ravine criteria. The mean age of participants was 42 ± 8.8 years, 66% of the participants were women, the mean eGFR was 62 ± 20 ml/min per 1.73 m-2, the patients were largely of Caucasian descent and hypertension was well controlled. The mean total kidney volume by MRI at baseline was 163.5 ± 97.8 ml. Tempos 2/4 was an open, not a double blind controlled study; historical controls of PKD were taken from the MDRD and CRISP studies by matching PKD patients for age, total kidney volume, eGFR, presence or absence of arterial hypertension and gender.

The Tempos 2/4 study found a substantial and significant reduction of the annualized total kidney volume growth rate in tolvaptan treated participants. Furthermore, the annualised eGFR slope was significantly less steep – i.e. improved – under tolvaptan treatment than in control. Reported common adverse events of taking tolvaptan were: thirst/increased drinking of fluids/pollakuria: in >50% of participants; intermittent blood creatinine increase – possibly from transient dehydration – in 13%.

From Tempo 2/4 to Tempos 3/4

The data from the Tempos 2/4 study were considered encouraging. They laid the foundation to a much larger phase III randomized controlled prospective double blind trial of 1445 patients with ADPKD-I by Ravine’s criteria, termed the Tempos 3/4 study. It was a 3-year trial conducted from 2008 to 2012. Participants were characterised by the following features: mean age 39 ± 7 years; male sex 51 %; white race 84 %; mean total kidney volume 1705 ± 921 ml; mean eGFR at baseline 81 ± 21 ml/min per 1.73 m-2; arterial hypertension controlled by antihypertensives 79 %. Not all patients completed the full 3 years of the protocol: in the tolvaptan group 23 % withdrew prematurely (controls: 13.8 % withdrawal rate). The drop out rate in tolvaptan treated patients appeared related to either thirst/polydipsia/polyuria or to transient abnormalities in liver function in 8.3 % of the 23 %. Treated patients had a choice of three different doses of tolvaptan: a high dose of 120mg/day (taken by 55 %), a medium dose of 90mg/day (21 %) and a low dose of 60mg/day (24 %). Adherence to study medication was better than 88 % in all. Two thirds of the participants were randomised to the active treatment group (tolvaptan), one third were in the control group. (VE Torres et al., NEnglMedJ,2012:367: 2407).

Interesting observations were made with regards to the slope of kidney function, assessed by the reciprocal of the serum creatinine concentration. The slope was -2.61 ml/mg per year in tolvaptan receiving patients compared to -3.81 ml/mg per year in placebo control. The annual difference in slope was 1.202 ml/mg (95% confidence interval 0.62 to 1.78, p<0.001), showing an improvement in the slope of treated patients. The difference (the improvement) was demonstrated for the entire group of all treated patients; it was also found for the subgroups of male patients; patients>35 years old; presence of eGFR <80 ml/min, 1.73 m-2 and eGFR >80ml/min, 1.73 m-2; patients with arterial hypertension; patients with a total kidney volume >1500ml. The difference (the improvement) could not be shown for female participants; for young patients under the age of 35 years; for PKD patients with normotension; for patients with total kidney volume <1500ml. An additional observation was made concerning renal pain; its incidence was significantly reduced by approximately 25% in tolvaptan treated patients.

Tolvaptan treatment in Tempos 3/4 was associated with an annual total kidney volume increase by 2.8% (95 % confidence interval 2.5 to 3.1). In contrast, the placebo control arm of the study found annual total kidney volume increase at 5.5% (95 % confidence interval 5.1 to 6.0, p<0.001), i.e. significantly higher. The reduced growth of cystic kidneys in tolvaptan treated patients was observed for the entire group of

Continued on page 26
Higher risk of cardiovascular disease

Renal and cardiovascular health after preeclampsia

Preeclampsia (PE) is one of the hypertensive disorders of pregnancy and a major cause of maternal and perinatal morbidity and mortality worldwide. Depending on the definition of PE used and the populations studied PE complicates up to 8% of all pregnancies. We estimate that at least 2.500 cases occur annually in the Netherlands. PE is characterized by hypertension and proteinuria occurring after the second half of pregnancy. Up to now the only cure is by delivery, often before or even remote from term. As a consequence PE is one of the major contributors to preterm births, which are known to be associated with lifelong health impairment in the offspring. Long-term vascular risk for the mother following PE has been recognized for many years, and recent data suggest that there is also an increased maternal renal risk.

The exact pathogenesis of PE is unknown, but is assumed to be multifactorial. Its pathophysiology involves activation of the inflammatory response including endothelial cell activation and dysfunction, immune mechanisms and altered endothelin. Its pathophysiology involves activation of the inflammatory response including endothelial cell activation and dysfunction, immune mechanisms and altered endothelin.

Long-term cardiovascular risk and prevention after PE

Long-term vascular risk following PE has been recognized since the 1960s. The relative risk of a diagnosis of hypertension in formerly preeclamptic women is 3.7. Apart from hypertension there is a higher risk of hypertension-related cardiovascular disease (CVD), i.e. 8-fold ischemic heart disease, cerebrovascular disease, and peripheral arterial disease. Prevention of CVD after PE is gaining more attention both in research and guidelines. Recent studies address lifestyle interventions to reduce the CVD risk. A guideline on treatment of CVD risk factors after PE is being developed. Currently, there is no systematic follow-up of women who had PE to allow evaluation of preventive measures.

One in four women will develop chronic hypertension after a hypertensive disorder of pregnancy. Still, there is no consensus about the management of hypertension in the immediate postpartum period and as a consequence when to discontinue or pursue the adopted management. Long-term blood pressure lowering aims to reduce the risk of cardiovascular disease, but this effect has not been unequivocally proven in young people. In the general population, systolic blood pressure lowering of 10 mmHg reduces the risk of stroke by 40% and of coronary heart disease by 20% in both primary and secondary prevention. The European Society of Hypertension and the Joint National Committee (JNC7) recommend the treatment of a blood pressure ≥140/90 mmHg in adolescents. More specifically, the American guidelines recommend blood pressure lowering treatment with ACE-inhibition when blood pressure is above ≥140/90 mmHg in formerly PE women. The possible benefit of treatment of a high normal blood pressure should first be evaluated in clinical research (1).

Kidney disease after PE

It has been suggested that PE itself increases the risk of CKD later in life. PE women have an 8-15 fold increased risk for developing ESKD, necessitating dialysis. From the 1960s to the 1980s, several biopsy studies found renal damage in formerly preeclamptic women. In many cases, the glomerular endotheliosis lesions, which are a typical feature of the kidneys in patients with PE, disappeared rapidly within 6 months. However, renal vascular lesions remained the same or changed only very slowly. Furthermore, renal vascular lesions were directly related to increased blood pressure. The finding that almost one-third of preeclamptic patients have microalbuminuria is important given the associated risks of microalbuminuria with both ESKD and CVD. Current UK recommendations refrain from screening women after PE when they do not have proteinuria 6-8 weeks post-partum. In the Netherlands we do not measure proteinuria routinely after delivery. Until now, few studies have reported renal function after PE. Estimated glomerular filtration rate (eGFR) and serum creatinine levels were not significantly different at early follow-up in women with and without PE (reviewed 2). It could well be that hyperfiltration is present shortly after PE but is not detected by eGFR calculation that is inherently more sensitive to loss than to gain of GFR. Indeed, results from renal hemodynamic studies indeed show higher filtration fraction (hyperfiltration) after PE compared to women with a history of normal pregnancy (Toering et al, abstract Society of Gynaecological Investigation 2014). It could be that this early hyperfiltration leads to renal damage and future hypofiltration, a pattern similar to the renal function loss in diabetes mellitus.

Future areas of research

Emerging evidence has changed our view on PE from being a syndrome unique and confined to pregnancy to a risk marker for CVD. Large epidemiological studies have shown that women with a history of preeclampsia have an increased risk of CVD. Such studies do not reveal the functional impact of a previous PE on several organs. The exact mechanisms for the increased CVD and renal risk are unknown. Logical common pathways are involved. Alternatively, PE itself induces permanent changes. Better understanding of the exact risk and identification of patients with the highest risk and need for follow-up and early prevention is needed.

References


Dr. Titia Lely, WKZ, Utrecht, The Netherlands

S17: Pregnancy and the kidney
Room:FORUM
Date: 01-06-2014
From 17:00 to 18:30

Dr. Titia Lely, WKZ, Utrecht, The Netherlands
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.

Grow your career with DaVita in Saudi Arabia.
Stop by the DaVita booth at ERA-EDTA or visit DaVita.com/SA.
One size does not fit all

Dialysate potassium concentration

Hyperkalaemia is the condition of potassium excess in the extracellular compartment, that occurs with a serum potassium value higher than 5.5 mmol/l. Hyperkalaemia is common in patients with end-stage renal disease, and because of its effect on cardiac conductivity, it is a topic of clinical relevance.

Potassium dietary intake in the interdialytic period is responsible for the frequent potassium overload of patients on maintenance haemodialysis therapy together with metabolic acidosis, that is mainly due to hydrogen ion generation by protein catabolism.

In healthy subjects, the stability of the potassium body pool is maintained by the renal regulatory excretion of potassium and a transient increase in kalaemia, following a dietary intake, triggers a transfer of potassium from the extracellular compartment to the intracellular one through the Na+/K+ pump, and thereafter the excretion by the renal tubular cells.

Haemodialysis removes K+ from the extracellular pool, but more than 60% of the potassium removed derives from the intracellular compartment. Thus it is obvious that potassium flux between these two compartments is fundamental in potassium removal during haemodialysis. The rate of this potassium flux can influence the cardiovascular tolerance to haemodialysis, because it could potentially trigger the cardiac arrhythmias. This clinical complication is at least in part due to the intradialytic increase of cellular membrane polarisation. Standard dialysis, using a fixed dialysate potassium concentration, determines a fall in kalaemia during the first hour of treatment, followed by a slow decrease. Redaelli, the leader on the field of our group, et al. in 1996 speculated that during the first hour of the dialysis session, there is an increased passive potassium diffusion through the cell membrane, related to a chemical gradient and a negative polarisation of the membrane itself.

The lower amount of potassium removal during continuous peritoneal dialysis in comparison to the removal during haemodialysis could suggest that potassium removal during haemodialysis could be too high and so hyperkalaemia could not due to an excessive potassium accumulation but at least partly due to an abnormal potassium distribution which requires appropriate corrections. In fact the more clinically impaired patients, whose cells have a small potassium content and a conspicuous sodium pool (sick cells), usually show hyperkalaemia more frequently than the patients in better clinical conditions. Therefore a high potassium gradient between the patient plasma water and the dialysate, could lead to an excessive potassium removal from intracellular compartment, causing cell sickness. A profiled dialysate potassium concentration could achieve a good correction of hyperkalaemia preventing a potassium depletion. In fact, Redaelli et al. reported in standard intermittent dialysis a dissociation between the amount of potassium removed during haemodialysis and pre-dialysis kalaemia levels.

Ciandrini et al. adopted a mathematical modeling approach to evaluate the effect of potassium removal on intracellular and extracellular K+ concentrations, using different potassium removal schedules with dialyses at fixed K+ concentration and at profiled K+ concentration. They correctly reported that K+ concentration is about 30-time higher in the intracellular compartment in comparison with the extracellular one and Na-K pump works in order to maintain this condition, moving K+ from the extracellular into the intracellular compartment. They also reported that Na-K pump performs its maximal role during the first hour of haemodialysis session when the kalaemia is at its highest level. In this phase potassium removal mainly derives from the extracellular space and there is a small potassium exchange ratio from the intracellular to the extracellular compartment. On the contrary, when the kalaemia value is less than 4 mmol/l, usually after 90 min from the start of haemodialysis, the Na-K pump decreases his flux exchange and consequently potassium flow from intracellular to extracellular space increases. In this phase, potassium removal mainly derives from the intracellular compartment without significant variations in kalaemia values. Thus the dialysate K+ concentration is mainly responsible for the variable activity of the Na-K pump during haemodialysis treatment and this affects the ratio between the intracellular and the extracellular potassium removal. Therefore, a K+ profiled haemodialysis should maintain the patient in a phase of high kalaemia for more time and as consequence potassium removal is mainly derived from the extracellular compartment. Conversely a K+ fixed haemodialysis leads to a potassium removal mainly deriving from the intracellular space.

At the end of dialysis session, potassium rebound takes place into the extracellular compartment in order to restore a balance between intra and extra cellular compartments with a consequent increase of extracellular K+ concentration and so of kalaemia. In conclusion a potassium profiled haemodialysis schedule could decrease the arrhythmogenic effect of haemodialysis by a intra-haemodialysis potassium removal. In 1992 Redaelli et al. reported in ‘The Lancet’ that, despite the high prevalence of ventricular arrhythmias in the haemodialysis population, these arrhythmias did not independently correlate with 4-year mortality and thus the high incidence of sudden death among haemodialysis patients remained unexplained. A possible explanation could be related to the relatively young age of those days haemodialysis patients. Nowadays we know very well that the arrhythmogenic effect of haemodialysis (particularly in patients with frequent and complex ventricular arrhythmias before dialysis), could be increased by a rapid decrease in the potassium plasma concentration, because of the consequent hyper-polarization of the resting membrane potential.

Up to now, we do not know how much K+ must be removed by dialysis in order to maintain a normal K+ body pool, but on the other hand, if we consider the progressive increase of the mean age of haemodialyzed patients, we could assume that the potassium dietary intake of these subjects is relatively low, which means that in these patients a standard dialysis accounts for an excessive removal of potassium, with consequent muscle mass impairment. So the dialysis goal in potassium management should not be the simply reduction of kalaemia, nullified by potassium rebound, but the control of potassium redistribution between intra and extracellular compartments, by the use of a profiled potassium dialysate concentration, and also the improvement of potassium pool, by enhancing the nutritional status of haemodialysis patients.

The problem of the progressive aging of patients on maintenance haemodialysis nowadays makes the potassium modulation an issue of extreme clinical relevance. It is necessary to avoid malnutrition that could be facilitated by severe dietary restrictions. On the contrary, we should encourage an adequate food intake, reserving to dialysis the task of redistributing the potassium from the extracellular to the intracellular compartment and removing only the true potassium excess. Moderate physical exercise should be associated to this clinical management, because it could increase patient’s lean body mass and thus potassium pool. Actually the electrolyte exchanges issue during haemodialysis is an hot topic in our Department and Drs. Di Filippo, La Milia, Manzoni, Violo and Pontoriero are in deep evaluating not only potassium but also calcium, bicarbonate and as a tradition sodium, in order to better define the kinetics of electrolytes during haemodialysis.

Francesco Locatelli, Lecco, Italy

S 14: A neglected issue in haemodialysis practice: haemodialysate.

Room: HALL 2
Date: 01-06-2014
From 17:00 to 18:30
Is it really a syndrome?

Chronic kidney disease – mineral bone disorder

In chronic kidney disease (CKD), alterations in circulating parameters of mineral and bone metabolism, such as calcium (Ca), phosphate (P), vitamin D, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23), are frequently present and associated with adverse clinical outcomes far beyond renal osteodystrophy. In 2006, these mineral and bone disorders (MBD) of CKD patients have been suggested to represent a specific entity, named CKD-MBD. The concept of Chronic Kidney Disease - Mineral Bone Disorder (CKD-MBD) does not appear to fulfill the requirements for a syndrome at first glance, but its definition has brought some clear-cut benefits for clinicians and patients, including wider and more complex diagnostic and therapeutic approaches to the management of this challenging set of issues. Admittedly, not all components of CKD-MBD are present in all patients at all times, but these are highly interrelated, involving mineral and bone laboratory abnormalities, clinical and histological bone disease, and finally cardiovascular disease. The presence of typical biological bone osteosclerosis processes in an ectopic anatomical location in CKD has helped to define the existence of an unprecedented bone-vascular relationship, extending its interest even to other medical specialties.

Influence on current guidelines

During the last decade, this novel concept has clearly influenced current clinical guidelines. NKF/KDOQI™ guidelines in 2003 for instance recommended that calcium-based phosphate binders should be avoided to treat hyperphosphatemia in the presence of cardiovascular calcifications. KDIGO in 2009 and other guidelines reinforced and extended this recommendation by stating that it is reasonable to choose oral phosphate binder therapy by taking into consideration other components of CKD-MBD.

Disorders of mineral metabolism and bone disease are common complications in CKD patients and they are associated with increased morbidity and mortality and decreased quality of life. However, to define CKD-MBD as a true ‘syndrome’ it is necessary to consider if it characterises a specific complication of CKD. While assessment of both mineral disorders and vascular or extraskeletal calcification are easily attainable, bone disease is less easy to diagnose. Since CKD-MBD is defined by the presence of abnormalities in any of the three components by which it is defined, diagnosis can be regarded as relatively straightforward but easily missed when histological-defined bone disease is the major or sole component. In contrast, the correct prognosis and treatment of this putative syndrome is much more complex. Several large observational studies indicate the importance of serum phosphorus control during CKD and how its control leads to favourable CKD-MBD prognosis. Furthermore, the importance of monitoring serum phosphorus control has also been formally acknowledged in the recent KDIGO guidelines. Following a successful diagnosis of CKD-MBD, current therapeutic approaches in the later stages of CKD before dialysis include dietary phosphate restriction or oral phosphate binder use or 1,25D treatment to improve 1,25D deficiency and secondary hyperparathyroidism. Use of phosphate binders and vitamin D activators has been well documented; however, evidence is mainly based on large epidemiological studies. There is a concerning lack of randomized controlled trials examining the effect of a specific therapy on prognostic and/or survival in this patient cohort. In summary to the original question, while the diagnosis of CKD-MBD can be regarded as relatively simple, the prognosis and therapeutic management of these patients still remains a complex task.

From a clinical point of view having the full-blown syndrome would intuitively be worse than having a single component. Numerous epidemiological studies associated all individual components of CKD-MBD to clinical outcome parameters, including mortality, even after correcting for renal function using estimated glomerular filtration rate (GFR). Moreover, several basic research studies have provided compelling evidence on a mechanism that may underlie potential causality between CKD-MBD components and disturbed outcome. However, since the concept of CKD-MBD was launched, no study has attempted to verify the relationship between any quantifiable levels of all its individual components (as a composite risk score) with clinical outcome. Furthermore, derangements in either direction (above or below target range resulting in J-curve or U-curve associations) can imply an increase in relative risk, making it even more challenging to ascribe a weight to a single deranged component. In summary, the question of added risk due to the presence of CKD-MBD is affirmative on a qualitative level, but is only based on historical cohort analyses.

Sustained impact in the nephrology community

After the definition of CKD-MBD in 2006, numerous guidelines have been published with recommended biochemical targets and therapeutic strategies aimed at obtaining a good clinical control of the condition. Furthermore, almost every National Society of Nephrology considered it necessary to make its position statement on the subject. Thus, the overall impact of the introduction of the concept “CKD-MBD” in the nephrology community has been both sustained and impressive. Not surprisingly, the resulting discussion has been centred on the applicability of the recommended biochemical targets, their reliability as surrogate markers of outcome and the probability that novel therapeutic approaches could actually result in the improvement of clinically important outcomes, such as cardiovascular complications and mortality.

The European Renal Association-European Dialysis Transplantation Association (ERA-EDTA) has recently founded a scientific working group on CKD-MBD, because of the potential beneficial impact of increased awareness of these disturbed components, but also because ERA-EDTA recognizes the huge scientific efforts that are required to bridge enormous gaps in knowledge and bring this to the bed-side of patients with CKD. As a scientific working group we believe that CKD-MBD is most likely to be of importance in terms of added risk to CKD patients, and that this additional risk can be targeted. Indeed as discussed above, in CKD patients the presence of CKD-MBD can be defined by easily accessible diagnostic criteria (with the exception of bone biopsy). However, the proof that one or few CKD-MBD components determine synergistically clinical outcomes is lacking.

In summary, our current opinion is, that CKD-MBD may have the potential to be defined as a true syndrome, however, it has not yet been demonstrated as having additive predictive value of its individuals components and still remains unproven that it is a modifiable risk factor.

Our assumption as a working group ‘CKD-MBD’ is that CKD-MBD has the potential to be defined a true syndrome, such as a constellation of concurrent signs and symptoms that suggest a common underlying mechanism for these components as opposed to the term disease. The term ‘syndrome’ also implies that in any patient at risk due to the presence of one or few components of the entire syndrome, the screening for additional components is highly recommended. However, it has not currently been demonstrated that there is an additive predictive value, which can be derived from identifying individual components.

Despite all we have learned about this putative syndrome, we have been left with only a hypothetical framework about how to treat patients. So while we agree that the concept of CKD-MBD has influenced, and continues to influence, our current clinical hypotheses, definitive proof of benefit of interventions in CKD-MBD is still lacking, and global–multiple therapeutic approach to treat simultaneously several components of CKD-MBD should be tested by well-designed new randomized controlled trials.
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