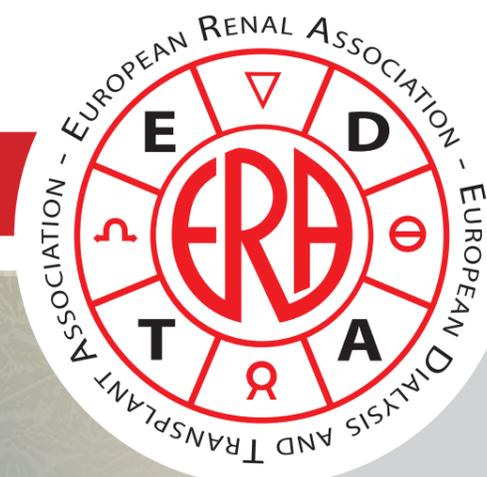




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DAILY CONGRESS NEWS

ISSUE # 3 MAY 23rd

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The Lancet

Symposium

The complications of dialysis and transplantation were the theme of today's *The Lancet* symposium, the latest evidence of the successful collaboration between ERA-EDTA and the Lancet/Lancet Diabetes and Endocrinology.

Professor Christoph Wanner discussed the multiple cardiovascular risk factors and profound structural changes to the heart and vascular tree that result in rapid development of cardiac and vascular disease, especially in younger patients. The adverse changes to the heart include left-ventricular hypertrophy (LVH) and dilatation with concomitant systolic and diastolic dysfunction, resulting in a greater risk of cardiac arrest in situations of stress, such as intradialytic hypotension and hypoxemia. As a result, cardiac and vascular mortality are several times higher in dialysis patients than in the general population.

The major cause of LVH and LV failure is fluid overload and, usually, hypertension. According to Professor Ercan Ok, volume and blood pressure control can be achieved without need for antihypertensive medication through longer and/or more frequent hemodialysis. It is also feasible with conventional hemodialysis by targeting *(continued on page 2)*

Late Breaking Clinical Trials



Alexander Zarbock, Germany

Early initiation of RRT in critically ill patients with AKI saves lives

Acute kidney injury (AKI) is a syndrome that affects 13 – 18 % of patients admitted to hospital and is particularly common in patients in the intensive care unit (ICU). The impact and prognosis vary considerably, depending on severity, acute and chronic comorbidities, and the timing of initiation of renal replacement therapy (RRT) also has an impact on the outcome. Zarbock et al. started a randomized study in which 231 critically ill patients with AKI and plasma neutrophil gelatinase-associated lipocalin >150 ng / ml were randomized. In 112 patients, RRT was initiated early (KDIGO stage 2), 108 patients received RRT later (in stage 3). As the study shows, early initiation of RRT in these critically ill patients with AKI pays off: Early initiation of RRT significantly improved 90-day survival, and this approach significantly reduced the plasma levels of pro-inflammatory mediators associated with an improved survival and renal recovery. Furthermore, duration of RRT and length of hospital stay were significantly shorter in the early group as compared to the late group. However, early initiation of RRT had no significant effect on requirement of RRT after day 90, organ dysfunction, and length of intensive care stay. ■



Hong Zhang, P.R. China

Steroid therapy in IgAN: Still open, if the benefits outweigh the risks

IgA nephritis (IgA nephropathy) is the most common glomerulonephritis. Glomerulonephritis (GN) constitutes the third most common defined cause of kidney failure in Europe, after diabetic and hypertensive nephropathy. Recent clinical guidelines recommend steroid therapy in patients with IgA nephropathy and persistent proteinuria but doubt has been cast on the value of this strategy recently. In the TESTING study, a randomized study by Zhang et al., 262 patients with persistent proteinuria >1 g / day and estimated GFR 20 – 120 ml / min per 1.73 m² were randomly assigned to receive 0.6 – 0.8 mg / kg / day of oral methylprednisolone (max 48 mg / day) weaning over 6 – 8 months, or matching placebo (after they had at least 3 months of supportive therapy including blood pressure control and renin-angiotensin system blockade). Time-averaged proteinuria after randomization was significantly reduced in the steroid treated arm (p < 0.001), and the primary composite renal outcome occurred in 8 participants (5.9 %) in the methylprednisolone group and in 20 participants (15.9 %) in the placebo group (p = 0.019). This benefit had its price, however, after a median follow-up of 1.5 years, serious adverse events occurred in 20 (14.7 %) vs. 4 (3.2 %) participants in the steroid and placebo groups, respectively (p = 0.001). The interim results suggest a likely renal benefit based on a modest number of events to date, and the ongoing long-term follow-up will help to further define the balance of risks and benefits. ■



Winfried März, Germany

Lipid apheresis only in patients without prevalent coronary artery disease?

Epidemiological studies suggest an association between Lp(a) levels and cardiovascular risk – which is why said marker has been addressed as a therapeutic target in all patients. März et al. analyzed the association between Lp(a) and CAD severity as well as long-term outcomes (median follow-up 9.9 years) in 3,313 participants undergoing coronary angiography in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Analysis of the results provides novel epidemiological and genetic evidence of Lp(a) being a risk factor for the development of CAD, but also shows that Lp(a) loses its association with outcomes in patients with prevalent CAD. These findings are backed up by replication in two similar, but independent cohorts (KAROLA and HCSS). Lipid apheresis is currently the only available approach for lowering Lp(a). The current data, however, do not provide support for this approach in CAD patients. Interventions to lower Lp(a) may be more successful in high risk patients before CAD becomes clinically manifest. ■

(continued from page 1) post-hemodialysis weight and promoting dietary salt reduction. Barriers include problems in assessing volume status and reducing post-hemodialysis body weight, and the need to convince the nephrology community that volume and blood pressure control do not usually require antihypertensives.

Dr Bruce Robinson reported that, based on national registry data, practices associated with improved survival in hemodialysis patients include high use of surgical vascular access (as in Japan and in some European countries) and longer or more frequent dialysis sessions that allow for more effective volume management. However, patient mortality remains high, especially soon after start of haemodialysis, and better preparation is needed that includes alignment of clinical decision-making with the wishes of patients and families to balance their quality of life with the burdens and benefits of treatment.

As immunological and infectious challenges are overcome, the risk of graft failure and mortality associated with post-transplant diabetes (PTDM) has become of increasing concern to nephrologists and patients. Dr Adnan Sharif explained that both insulin resistance and β -cell dysfunction contribute to PTDM, but controversy remains concerning their relative importance and whether PTDM is a distinct entity or a variant of type 2 diabetes. There is a continuing need for more data on the incidence and clinical outcomes of PTDM, and the role of glycemic control and of diabetic therapies in prevention and management.

All articles are now available at www.thelancet.com. ■



Annette Bruchfeld, Sweden

Chronic infection with the hepatitis-C virus (HCV) can be both a cause and a potential complication of chronic kidney disease. One major problem is that only limited options are available for treating HCV infection in patients with advanced kidney disease. Medications such as Sofosbuvir can only be used, if the estimated glomerular filtration rate (eGFR) is >30 ml/min/1.73m², because it is mainly eliminated renally. Ribavirin should also be used with caution in cases of severe renal insufficiency. An all-oral ribavirin-free regime has now been tested in a study by Bruchfeld et al., in which 224 CKD patients (in stage 4 or 5) were randomized and received either elbasvir / grazoprevir (EBR / GZR) or a placebo. Placebo patients (deferred treatment group, DTG; N=113) received EBR / GZR after placebo therapy. The study showed that administration of EBR / GZR for 12 weeks was highly effective, with a low rate of adverse events in patients with CKD and HCV G1 infection. Even patients with HCV genotype 1a (GT-1a) and baseline resistance-associated variants (RAVs) had only a modest decrease in efficacy. ■



Hilary Riva, Switzerland

All-oral, ribavirin-free regimen successful in hepatitis-C patients with chronic kidney disease

Chronic infection with the hepatitis-C virus (HCV) can be both a cause and a potential complication of chronic kidney disease. One major problem is that only limited options are available for treating HCV infection in patients with advanced kidney disease. Medications such as Sofosbuvir can only be used, if the estimated glomerular filtration rate (eGFR) is >30 ml/min/1.73m², because it is mainly eliminated renally. Ribavirin should also be used with caution in cases of severe renal insufficiency. An all-oral ribavirin-free regime has now been tested in a study by Bruchfeld et al., in which 224 CKD patients (in stage 4 or 5) were randomized and received either elbasvir / grazoprevir (EBR / GZR) or a placebo. Placebo patients (deferred treatment group, DTG; N=113) received EBR / GZR after placebo therapy. The study showed that administration of EBR / GZR for 12 weeks was highly effective, with a low rate of adverse events in patients with CKD and HCV G1 infection. Even patients with HCV genotype 1a (GT-1a) and baseline resistance-associated variants (RAVs) had only a modest decrease in efficacy. ■

Pre-emptive marsupialized catheter can increase PD prevalence in elderly dialysis patients

The percentage of patients who decide on peritoneal dialysis (PD) is relatively small – less than 10 % in most European countries. PD is equally valuable as a form of dialysis and in terms of outcomes is not inferior to in-center hemodialysis. On the contrary – due to its gentle and continuous removal of fluids, PD imposes less stress on the circulation system, for which reason it may also be more appropriate for many elderly patients, who frequently have cardiovascular problems on HD. The percentage of PD patients in this group is very low, nevertheless. The study by Riva et al. showed that pre-emptive insertion of a PD catheter, marsupialized in this case, can significantly increase PD prevalence in this PD population at a GFR of 15 – 10 ml/min/1.73m² (from 8 % to 19 %). ■

ERA-EDTA MEMBERSHIP INFO

General Assembly

ERA-EDTA Members don't miss the ERA-EDTA General Assembly which will take place today from 09.30 to 10.45 in Hall G, Level-2, Austria Center Vienna.



Admission is strictly reserved to ERA-EDTA members only. Please have your ERA-EDTA membership card and badge ready in order to enter the Hall.

Important notice: Only Full ERA-EDTA members have the right to vote.



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ERA-EDTA Membership Desk info



Do you know all the benefits for ERA-EDTA Members? Check them out and become a member today!

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53rd CONGRESS ERA-EDTA VIENNA AUSTRIA MAY 21st-24th, 2016



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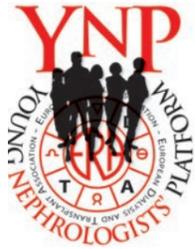


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Tomorrow's nephrology presented by the nephrologists of tomorrow



ANA CARINA FERREIRA
Lisbon, Portugal
Chair of Young Nephrologists' Platform

The ERA-EDTA's Young Nephrologists' Platform (YNP) will hold its session entitled 'Tomorrow's nephrology presented by the nephrologists of tomorrow', on 24th May, from 1.15 – 2.45 pm. The session will start with an update on YNP initiatives, provided by Dr. Ana Carina Ferreira, the current YNP Chair.

The YNP was developed in 2012 and commenced its formal activities in 2013. It aims to involve all young professionals with an interest in nephrology in all the activities of the ERA EDTA. It currently has 219 members from nearly all European countries. All ERA EDTA members who are less than 40 years old and have presented at least one abstract at an international meeting can apply to become a YNP Ordinary Member, and thus start benefiting from the various activities of the platform. Over the past year, YNP, together with the ERA EDTA Immunonephrology Working Group (IWG), organized its second CME course entitled 'Novel Biomarkers in Glomerulonephritis', which was held in Istanbul. In 2016, YNP has already opened registration for its third CME course, about 'Pregnancy and Kidney Disease'. This course will be held in Lisbon, Portugal, on September 22 and 23 (please visit: http://era-edta.org/YNP_CME_Course2016_Pregnancy_and_kidney_disease.html). A week later (September 29 and 30), YNP will travel to Wroclaw in Poland for its fourth course, this time on 'Interventional Nephrology'. YNP members pay low fees to register for these courses.

Besides its various courses, YNP has other initiatives which benefit young people, such as the YNP Advisory Program. This program offers young nephrologists a unique opportu-

nity to exchange experience and to confer with senior scientists/professionals within the Society. Four advisor / advisee pairs have already completed their cooperation and have provided very good feedback about it. YNP also supports young nephrologist by granting up to 50 free ERA-EDTA memberships (abstract-based and paper-based grants), but only to YNP members. In addition, YNP has launched 'Hot Topics', a direct channel to experts in specific areas. On a bimonthly basis, YNP board members choose a topic and invite an expert to comment and discuss a recent and important paper on the topic. This is published in both NDT-Educational and the YNP webpage, and all users are invited to add questions and comments, and to enter into a dialogue and to network with the experts. There are also quizzes at the end of each topic, in which all members can test their knowledge. Finally, in 2017 there will be two vacancies on the YNP Board. If you are an ERA-EDTA member no older than 37, have presented three abstracts as the first author at international meetings, and if you want to help develop the platform, be aware of the open call next year!

But the session doesn't end with this update. It will be our pleasure to announce and listen to the 2016 winner of the Stanley Shaldon Award, Dr. Emilie Cornec-Le Gall, from France, who will discuss the possibility of personalized treatments for APKD patients. From genetic diseases we will turn to AKI and Andreas Linkermann from Germany, who will deliver a lecture entitled 'Let's talk about death! Regulated necrosis in acute kidney injury', before we then move to the transplant field, where Oriol Bestard from Spain will talk about 'Immune monitoring in kidney transplant recipients'. Finally, we return again to the genetic (but rare) diseases with David Kavanagh from the UK, who will talk about 'Recent developments in atypical haemolytic uraemic syndrome'. For further information, please visit our webpage or email us at ynp@era-edta.org. ■

Expert in Interview



Young Nephrologists' Platform (YNP)

The Young Nephrologists' Platform (YNP) was developed in 2012 and commenced its formal activities in 2013. It aims to involve all young professionals with an interest in nephrology in all the activities of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA). It is composed of 9 Board members: 6 elected members from the ERA-EDTA plus 3 ex-officio members, winners of the annual Young Investigator award.

All young (< 40 years old) ERA-EDTA members can apply to become Ordinary Members, and these are the ones who benefit from YNP activities.

Communication among members is by electronic means, in the form of blast emails, surveys, and by using the YNP blog. Over these last three years, YNP has developed two programs (free membership program and the advisory program), prepared the annual sessions at the European congress as well as annual CME courses, and has developed a new educational tool called 'Hot Topics' (see below).

The Free Membership Program offers 50 ERA-EDTA memberships to YNP Ordinary Members, based on two types of accomplishments: the abstract-based type (30 free memberships to the 30 best abstracts submitted to annual ERA-EDTA Congress) and the paper-based type (20 free memberships for manuscripts published in ERA-EDTA journals by YNP members as the first or last author).

The Advisory Program is a unique, 9- to 12-month opportunity to exchange experience and knowledge between two participants, the advisor (an experienced nephrologist, member of the ERA-EDTA) and the advisee (a young professional and YNP member).

The YNP sessions at the ERA-EDTA annual congress are organized in such a way as to provide young recognized researchers an opportunity to showcase their experiments and results. Every year, the Young Investigator Awardee is also invited to lecture during the YNP session.

The YNP CME courses focus on different topics each year.

Hot Topics are seen as a new study resource and were developed to help young physicians not only to gather the latest information on certain themes, but also to interact with renowned experts. On each topic, YNP invites an expert to discuss a recent and relevant paper, and all YNP members can participate and communicate with the expert, via blog, adding questions or comments. YNP members can also test their knowledge with the YNP quizzes we provide on each topic. ■

Symposium 49

YNP – Tomorrow's nephrology presented by the nephrologists of tomorrow
Tuesday, 13.15 – 14.45, HALL D

THE HOT TOPICS – don't miss them!

The Young Nephrologists' Platform (YNP) is growing and developing some new and exciting activities aimed at delivering educational programs and facilitating communication among young European nephrologists.

The most recent program to be launched is Hot Topics, a direct channel to experts in specific areas. This scheme was developed to help young (or even older!) nephrologists acquire the latest information on certain topics in nephrology and to interact with renowned experts.

On a bimonthly basis, the YNP Board chooses a theme or topic to be published. Then we start working! For each topic, we write a short text outlining various key points relating to the topic; we provide some further details or unknown news about it (in the section Did you know that ...); we post an image (when feasible); and finally, we choose an article about the topic and in-

vide an expert to discuss the article in question (Meet the expert section). Very simple!

These Hot Topics are then published on both the YNP and NDT-Educational websites. Once published, any NDT-Educational user can participate, via the NDT-Educational blog, by adding questions, comments, or anything they feel may be important. This is a unique opportunity to have an open dialogue and to network with the experts. On top of that, nephrologists (not only the younger ones) can test their knowledge by taking the YNP quizzes.

So now that you understand the concept, we invite you to visit our webpage (<http://www.era-edta.org/page-19-217-0-217-hottopics.html>) and participate! We have already produced a number of topics: aHUS, renal fibrosis, and amyloidosis. FGF23 is coming next! ■



CLAUDIO RONCO
Vicenza, Italy

Prof. Ronco, let's start with a rather provocative question: Why is a wearable artificial kidney necessary – taken into account that we do have peritoneal dialysis and even home hemodialysis?

RONCO: Well, that is easy to answer: We have to be visionary! Have a look at other medical disciplines and how they use and develop technologies. Cardiology, for example: In the past, cardiac pacemakers had been rather large and then they were reduced in size, volume and weight. They became wearable and, finally, they became implantable. Nowadays a modern pacemaker is not bigger than a two Euro coin. I believe we have to develop technologies in order to improve the attractiveness of our discipline for young doctors. Stagnancy is death – and we need visions and inventive imagination to further enhance nephrology. Besides, in developing miniature dialysis devices, we want to free the patients from a large machine or the constraint to be in bed or at home. Also continuous ambulatory peritoneal dialysis (CAPD) involves multiple fluid exchanges during the day, which complicates life a lot. Our vision is to enable end stage renal disease patients to live a more carefree life – with a portable device doing its job while the patient can work, eat, sleep or go for a walk. The option to completely free the patient from any dependence from a machine one day by developing an implantable device is absolutely appealing.

How far is the development of such a device compared to the progress that has been made in pacemaker technology?

RONCO: Compared with the pacemaker technology we are miles behind. But of course, we have to consider that pacemakers are rather "simple" electronic devices. An artificial kidney is much more complex, it also has to include a hydraulic component. And we started much later to think about a portable dialysis device. The development of a wearable pacemaker began in the 1940s and that of implantable devices in the 1950s / 60s. We started to think about a portable artificial kidney in this millennium. The first wearable ultrafiltration device developed by Victor Gura in Los Angeles / US was

Looking into the Future: "The Wearable Artificial Kidney is on its way"

Interview with Professor Claudio Ronco

tested in Vicenza in 2006. Gura has refined his original device now and last year he passed the first FDA-approved proof-of-concept trial with an artificial kidney. So the first prototype is now looming on the horizon. We are working on a wearable artificial kidney, too. But we have taken different paths. First of all, we concentrated on a wearable, portable ultrafiltration device, which is basically designed to control fluid overload only. Here at the International Renal Research Institute of Vicenza (IRRIV) we have made considerable progress and we hope to enter the clinical testing phase quite soon. Much more complicated is the development of a device that is also able to purify blood. This is under evaluation and we faced many technical challenges, but we are exploring some interesting new technologies that might solve the problems. So I am quite optimistic that we can test the device in clinical practice in two or three years. The wearable artificial kidney is on its way!

What are the biggest challenges in developing a miniaturized dialysis device?

RONCO: The biggest challenge remains the vascular access. This is the most important part of every extracorporeal therapy. It has to be safe as well as adequate and efficient. The good thing is that we need a much lower blood flow compared to classic chronic dialysis, because wearable techniques are designed to work for 12 or 24 hrs a day. So we have to design a special vascular access for this purpose. But a miniature device requires the re-development of several components: In this moment we are working on smart circuits and pumps. The device has to work with small quantities of fluids that have to be recirculated and regenerated. One of the issues that we are facing here is to try to develop a non-thrombogenic circuit, so that there is no risk of clotting. Other challenges are the energy supply, safety components and a smart and easy to handle information technology interface. Apart from these technical challenges, the funding of the development is also a problem.

Really? I thought companies that produce dialysis machines should have a very strong interest in your development...

RONCO: Well, we approached the "big names" in this branch of industry, but the interest was very tentative. I do not know, if that was because they have invested a lot in the existing

systems and want them to be state-of-the-art as long as possible or because they have their own projects and are developing similar miniaturized devices. Anyway, we will proceed – and maybe the interest will grow then – like it was with our baby dialysis machine: At the beginning, no industry partner was interested, but when it was nearly ready-developed, the interest grew very strong.

Let's come back to your wearable ultrafiltration device. You pointed out that blood flow rates are lower. Does this involve any medical advantages?

RONCO: We reduce the efficiency, but we prolong the time of application. Therefore the wearable device works more like the biological kidneys and this has advantages: If you remove fluids slowly and gently over a long period of time, the patient does not suffer from hemodynamic instability we often see in chronic intermittent dialysis. So especially for patients which are affected by combined kidney and heart failure, the so called cardio renal patients type 4, this might be beneficial, the slow removal of fluids might improve heart performance and contractibility.

Do you see chances that in, let's say 10 years' times, we have artificial kidneys which can be implanted?

RONCO: Dr. William H. Fissell, an expert from the US, has already presented preliminary experiments on implantable devices. I think that this is one direction that is of interest and that we might see more in the next years to come. But I do not believe that we will have a full working implantable device in the next ten years. Maybe we have good and efficient wearable devices in clinical practice then. This is what we should be aiming at – and then we should take the next steps. The research in miniaturized devices may also provide unexpected results applicable in current technology. This is typical of a stepwise process of (r)evolution of a medical field. And while we are trying to optimize the technology and make it possible to have an efficient portable dialysis machine allowing the patient to move around during treatment we nephrologists should concentrate on another important challenge: We have to improve prevention strategies. The best option for a CKD patient is still to prevent him from ending up as a dialysis patient – no matter if dialysis machines are as they are today, portable or even implantable! ■



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How can they live happily together?

Exploring the relationship between the gut microbiota and the kidney in IgA nephropathy



**LORETO GESUALDO
AND HIS TEAM**
Bari, Italy

Humans are now regarded as 'super-organisms', the result of a parallel evolution with their own indigenous symbiotic microbiota. The human gut microbiota is a very complex consortium of trillions of microbes, whose collective genome ('microbiome') contains at least 100 times more genes than our eukaryote genome. At least 1000-1150 different species are harbored in the human intestinal ecosystem.

Bacteria chemically interact with each other and the host through substrate fermentation and metabolite production. Through a complex microbial-mammalian cometabolism, the gut microbiome has evolved to exert a marked influence on the human metabolic phenotype. Indeed, the role of the intestinal ecosystem in keeping the human body in good health is increasingly acknowledged. The gut microbiota is involved in protection against pathogens, education of the immune system and modulation of gastrointestinal development. The intestinal mucosa works as a barrier against antigens and pathogens, and the gut microbiota is involved in maintaining its integrity, by (i) improving tight junction efficiency, (ii) producing antimicrobial substances and / or by (iii) upregulating mucin-related genes. On the other hand, intestinal microbes play a pivotal role in the etiology and pathophysiology of a variety of diseases. By way of example, alterations in the composition of gut microbiota (namely 'dysbiosis') are associated with, but are not limited to, inflammatory bowel diseases (IBD), irritable bowel syndrome, allergic diseases, type 1 and type 2 diabetes, and celiac disease or sprue.

IgA nephropathy (IgAN) is the most common primary glomerulonephritis. Progression toward end-stage renal disease (ESRD) is observed in 25% to 40% of IgAN patients and no specific treatment is currently available to prevent progression. The demonstration of a presumptive role of the gut mi-

crobiota in IgAN development has recently been shown in BAFF (B-cell activation factor of the tumor necrosis factor family) overexpression in transgenic mice (BAFF-Tg), which develop commensal bacteria-IgA associated nephropathy. Moreover, of interest is a possible correlation between lipopolysaccharide (LPS) exposure and defective galactosylation of IgA, based on a study of cultured peripheral B lymphocytes from IgAN patients.

Bacterial dysbiosis at salivary and / or fecal level has been evidenced in IgAN patients with progressive (P) and non-progressive (NP) disease in comparison to healthy subjects (HC). Compared to HC and NP, a lower salivary and fecal microbial diversity was found in P IgAN patients (see Figure 1). Compared to HC, several beneficial microbial groups (for example, species belonging to *Lactobacillus* and *Bifidobacterium*) were reduced in fecal samples of NP and were even lower in P patients. At the same time, several potentially harmful bacteria (for example, *Enterobacteriaceae* species) were increased in P patients compared to NP and HC subjects. Consistently, the amount of fecal and urinary microbial metabolites (for example, free aminoacids, short-chain fatty acids [SCFA], esters, aldehydes, etc.) also differed between healthy subjects and IgAN patients, with a marked difference in progressors. Recently, it was shown that transplantation of intestinal microbiota from IgAN P and NP into the humanized mouse model of IgAN (α KICD89 transgenic mouse) was able to modulate the renal phenotype, in particular IgA1 deposition. Additional evidence supporting a close intestine-kidney connection in IgAN comes from a genome-wide association study. This identified multiple susceptibility loci in IgAN, which are associated with the risk of IBD or with the maintenance of the intestinal epithelial barrier and the intestinal immune response to mucosal pathogens. Moreover, the genet-

ic risk strongly correlated with variation in local pathogens, particularly helminth diversity.

An increased intestinal permeability has also been shown in IgAN patients. Intestinal permeability was correlated with soy IgA antibodies suggesting, at least in a subgroup of patients, an intestinal dysfunction leading to the production of IgA against food antigens. Additionally, small bowel inflammation, despite normal morphology, has been observed in IgAN patients. It is then arguable that a defective immune tolerance might favor an abnormal response to microbiota, with alteration of the intestinal barrier, increased antigen absorption and subclinical intestinal inflammation. Interestingly, evidence in the literature shows the effect of dietary patterns on microbiota composition and particularly on the salivary, fecal, urinary and plasma metabolome. Several microbial metabolites, such as SCFA mainly derived from complex carbohydrate fermentation, improve intestinal barrier integrity and show an immune-modulating activity by inducing transcriptional responses in immunity cells. Compared to the Western diet, the Mediterranean diet (rich in fiber and vitamins, and low in animal proteins and fats) drives the microbial metabolic balance toward a saccharolytic profile and promotes a general healthy status. This could be of crucial importance in IgAN patients, since proteolytic fermentation leads to the production of several noxious compounds, such as p-cresol and indoxyl sulphate. These compounds are recognized as the main microbial uremic toxins associated with chronic kidney disease progression and comorbidity, promoting inflammation, oxidative stress and cardiovascular complications. They are also associated with increased mortality in nephropathic patients, thus emerging as novel markers predicting the progression of cardiorenal disease.

As a future perspective in this interesting area of research, efforts are still required to investigate the relationship between IgAN and the gut microbiota. We also need to investigate new putative therapeutic and preventive tools, including non-pharmacologic, nutritional approaches to the management of IgAN. ■

References

1. Floege J, Feehally J. *Nat Rev Nephrol* 2016; 12(3): 147-56
2. Coppo R. *Nephrol Dial Transplant* 2015; 30(3): 360-6
3. McCarthy DD et al. *J Clin Invest* 2011; 121(10): 3991-4002
4. Kiryluk K et al. *Nat Genet* 2014; 46(11): 1187-96
5. De Angelis M et al. *PLoS One* 2014; 9(6): e99006
6. E. Montemurno et al. *Microb Ecol* 2015; 70(2): 557-65
7. Lauriero G et al. Putative role of microbiota in the progression of IgAN. Abstract at 53rd Congress of ERA-EDTA 2016
8. Ito S et al. *Toxins* 2014; 6: 665-678

Symposium 29
The gut-renal axis
Monday, 15.15 – 16.45, HALL A



MANUEL PRAGA
Madrid, Spain

Is acute interstitial nephritis an overlooked cause of AKI?

AIN is increasingly prevalent and most often drug induced

The true incidence of acute interstitial nephritis (AIN) is difficult to estimate accurately due to several factors. On the

one hand, the diagnosis of AIN is based on the demonstration by renal biopsy of the characteristic changes that define the disease: inflammatory interstitial infiltrates accompanied by interstitial edema, whereas glomeruli and vessels are typically normal. The infiltrates are composed by lymphocytes, macrophages, plasma cells and eosinophils. Since AIN is more common in elderly and hospitalized patients with varying degrees of frailty, many doctors prefer to adopt a pragmatic attitude, discontinuing the theoretically causa-

tive drug without performing renal biopsy and in some cases prescribing a short course of corticosteroids.

On the other hand, some epidemiologic studies suggest that a significant proportion of cases may have a subclinical asymptomatic course, going unnoticed but leaving in many cases an irreversible kidney damage. Recent studies have pointed out the role of agents like nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs)

in the increasing incidence of AIN [1]. Interestingly, AIN episodes related to NSAIDs and PPI are frequently asymptomatic and without a clear chronologic correlation with the onset of these treatments, making it more problematic to establish a correct diagnosis. Finally, the offending drug is difficult or impossible to identify, particularly in elderly poly-medicated patients in whom uncontrolled consumption of NSAIDs and PPIs is common.

Several studies have reported that AIN represents 5-18% of renal biopsies performed in the setting of acute kidney injury (AKI) with a tendency to increase. A recent publication of the Spanish Registry of Glomerulonephritis [2] analyzed more than 17,500 native kidney biopsies performed in the period 1994-2009. The prevalence of AIN increased from 3.6% in the first 4 years to 10.5% in the last period analyzed. Notably, this increase was particularly striking among elderly patients (>65): from 1.6% to 12.3%. Other studies from other countries have reported a similar tendency. Thus, a recent study from the Mayo Clinic [3] compared 45 elderly patients (≥ 65 years) and 88 younger adults (18-64 years old) with biopsy-proven AIN. The elderly had significantly more drug-induced AIN than younger patients (87% versus 64%), antibiotics and PPI being the most common offending drugs in the former. The elderly had also more severe AKI and more need for dialysis.

In most countries, particularly in those where registries are available, drug-induced AIN (mainly related to antibiotics and NSAIDs) accounts for the vast majority of cases. However, it is important to remark that in less developed countries, infectious AIN is still an important cause of the disease.

Initial descriptions of AIN drew a characteristic clinical picture, with a remarkable presence of skin rash, fever and eosinophilia. By contrast, more recent series [4] show that this classic diagnostic triad is present in only 10-15% of the patients. AKI is present in practically all the cases and accompanied by arthralgias (45%), fever (36%), medicamentous skin rash (22%) and peripheral eosinophilia (35%). However, as stressed above, elderly patients with NSAID- or PPI-in-

duced AIN can be even more oligosymptomatic, and eosinophilia is frequently absent. Therefore, is very important to maintain a high level of suspicion of AIN in patients with AKI of unknown etiology, particularly in poly-medicated elderly patients. The presence of sterile leukocyturia and leukocyte casts is very common in AIN (82% in the last series), whereas nephrotic-range proteinuria is uncommon with the exception of some NSAID-induced AIN.

To establish the cause of AIN in cases not related to drugs is often difficult. Systemic diseases (sarcoidosis, Sjögren syndrome, IgG4-related disease) tubulointerstitial nephritis with uveitis (TINU), AIN caused by antibodies directed against tubular basement membrane antigens and, in underdeveloped countries, infectious AIN are the main causes to consider.

Withdrawal of the culprit drug is the mainstay of treatment in drug-induced AIN. However, several studies suggest that early administration of corticosteroids can speed the recovery of renal function and decrease the risk of residual CKD. The Grupo Madrileño de Nefritis Intersticiales performed a retrospective multicentre study in 61 patients with biopsy-proven, drug-induced AIN. A majority of patients (85%) received corticosteroids and their long-term outcome was significantly better than that of patients who did not (final proportion of patients on chronic dialysis 3.8% versus 44%). But the most important finding in this study was the close correlation between the delay in the onset of corticosteroids and renal function recovery.

Among the patients who had received corticosteroids, a complete recovery of baseline renal function was observed in 53%. When comparing these patients with the remaining 47% in whom renal function recovery had been only partial, no differences in baseline characteristics nor in the doses or duration of corticosteroids were found. However, a significant difference in the interval between drug withdrawal and onset of corticosteroid treatment was observed (13 ± 10 versus 34 ± 17 days), as well as a significant correlation between the delay in corticosteroid treatment and the final serum creatinine. By multivariate analysis, an interval

longer than 7 days between drug withdrawal and onset of corticosteroid treatment and the severity of interstitial fibrosis were the only clinical factors that significantly increased the risk of an incomplete recovery of baseline renal function. Repeated renal biopsies in this study showed a rapid transformation of interstitial infiltrates into areas of irreversible fibrosis.

These data prompted us to establish in our hospital the following therapeutic protocol in patients with drug-induced AIN:

1. Rapid identification and withdrawal of the offending class.
2. Early administration of corticosteroids (<5 days after diagnosis) unless there is rapid renal function recovery after drug withdrawal in mild cases. We usually administer 3 intravenous pulses of methylprednisolone, 250 mg each, followed by oral prednisone 1 mg/kg/day for 1-2 weeks. Prednisone is then tapered down for 4-6 weeks.
3. When renal function does not improve after 2 weeks of treatment, corticosteroids are discontinued more rapidly. However, it is important to remark that the efficacy of corticosteroids in AIN has not been evaluated by means of prospective controlled trials. ■

References

1. Praga M et al. Nephrol Dial Transplant 2015; 30: 1472-1479
2. Goicoechea M et al. Nephrol Dial Transplant 2013; 28: 112-115
3. Muriithi A et al. Kidney Int 2015; 87: 458-464
4. Praga M, González E. Kidney Int 2010; 77: 956-961.

Symposium 32

AKI – pathophysiology and definition
Monday, 15.15 – 16.45, HALL F

Antifibrotic therapies for CKD: where are the trials?

It is essential to bridge the 'Valley of Death' between science and the clinic

Chronic kidney disease (CKD) is a major health and economic burden with a rising incidence. During progression of CKD, the sustained release of proinflammatory and profibrotic cytokines and growth factors leads to an excessive accumulation of extracellular matrix. Transforming growth factor β (TGF- β) and angiotensin II are considered to be the two main driving forces in fibrotic development. Blockade of the renin-angiotensin-aldosterone system (RAAS) has become the mainstay therapy for preservation of kidney function, but this treatment is not sufficient to prevent progression of fibrosis and CKD. Several factors that induce fibrosis have been identified, not only by TGF- β -dependent mechanisms, but also by TGF- β -independent mechanisms. Among these factors are the (partially) TGF- β -independent profibrotic pathways involving connective tissue growth factor (CTGF, also known as CCN2), epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) and their receptors (EGFR and PDGFR, respectively). Although TGF- β is generally considered to be the driving force behind fibrotic processes, alternative factors such as CTGF, PDGFR and EGFR signaling pathways have been identified as feasible targets for treatment of CKD and kidney fibrosis. Interaction between these pathways is exemplified by observations that induction of CTGF expression by TGF- β is partially EGFR dependent and that Ang II-mediated EGFR transactivation in renal epithelial cells is associated with concomitant TGF- β activation. Furthermore, CTGF is upregulated by, and is itself a ligand for, EGFR activation, which might constitute a positive feedback loop.

In addition, TGF- β requires both PDGFR and EGFR for its profibrotic activity, and dual blockade of PDGF and EGFR pathways with imatinib plus lapatinib prevented fibrosis to a greater extent than either drug alone.

Numerous studies have demonstrated the successful application of direct or indirect blockade of the CTGF, PDGFR and EGFR signaling pathways to prevent experimental kidney fibrosis, but none of these treatment strategies has yet been translated into the clinic. One reason for these failed attempts could be the toxic effects of these drugs in patients; for example, the adverse effects that have been reported in phase I clinical trials or potential threats based on preclinical observations.

Among others, CTGF, PDGFR and EGFR all seem to constitute valid alternative targets to TGF- β , especially if concerns regarding the risks associated with blocking the beneficial anti-inflammatory and tumor-suppressive actions of TGF- β prevent clinical implementation of TGF- β inhibitors. On the basis of current literature, it is difficult to prioritize between these alternative targets. However, considering their substantial interaction, it seems that targeting multiple growth factors might represent the best strategy for treatment of kidney fibrosis [1].

Although CKD can originate from a wide variety of primary and secondary forms of kidney injury, they all have in common that fibrosis increases gradually. This phenomenon



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Utrecht, The Netherlands

is considered responsible for progressive loss of functional kidney tissue and physiology. Over the past decades understanding of the nature of fibrosis and CKD progression has consistently increased, which has led to impressive, ever-growing lists of possible therapies and successful interventions in preclinical studies. In this respect, there is not much difference between the science of CKD and that of other fibrotic diseases like, for example idiopathic pulmonary fibrosis (IPF). However, the translation of the accumulating understanding of the pathogenesis of CKD into clinical trials appears to seriously lag behind that of IPF.

For example, while the Food and Drug Administration (FDA) recently approved nintedanib and perflinone in IPF, these novel drugs have not or have hardly *(continued on page 8)*

(continued from page 7) been tested as treatments for CKD in patients, although the pathways addressed would seem equally relevant. Moreover, since the approval of pirfenidone and nintedanib, several other innovative drugs are already being tested in IPF trials, including ambrisentan, ti-pelukast, Novartis QAX576 (a humanized IL13-specific mAb) and GSK3008348 (an alpha V beta 6-blocker).

The huge prevalence and increasing incidence of CKD, its serious impact on quality of life and productivity, as well as the huge costs associated with the condition would seem to provide a very attractive market for novel antifibrotic drugs. However, there are several compelling reasons why pharmaceutical companies seem to favor diseases other than CKD for trials of these drugs. In the first place, given the options for renal replacement therapy, CKD is not a lethal disease, unlike IPF. This increases the threshold for the acceptance of costs and adverse side-effects, and lowers the chance for rapid approval. Also, following the widespread implementation of RAAS inhibition as a cornerstone of CKD treatment, the rate of progression towards end-

stage renal disease is relatively slow. Therefore, endpoints are difficult to reach within acceptable time frames [2].

A further issue might be that the kidney, as the second most complex organ of our body, is susceptible to a very diverse range of pathogenesis modifiers, making it very difficult to build well-matched study groups for comparative efficacy testing. Moreover, the pharmacokinetics of many drugs might be significantly influenced by kidney diseases that affect protein retention, filtration rate, and tubular metabolic and excretory functions, so raising concerns about dosing adjustments.

Last but not least, there is growing awareness in industry that the relevance or reliability of highly published (and cited) scientific evidence for efficacy and safety in preclinical models is disappointingly limited, given the less than 50% successful attempts at inhouse reproduction. No doubt this adds to the 'Valley of Death' between fundamental science and successful translation of its discoveries into clinical trials, favoring an emphasis on limiting cost by first aiming for approval for narrower indications [3, 4].

In aggregate, the above implies that we may need to be patient, but that we also need to be inventive and persistent in developing reliable secondary endpoints and getting these accepted by the regulatory authorities. We also need to secure and increase our reputation as reliable scientists, thereby increasing the appreciation of CKD and kidney fibrosis as attractive areas for clinical development of novel drugs. ■

References

1. Kok HM et al. Nat Rev Nephrol 2014; 10(12): 700-11
2. Perez-Gomez MV et al. J Clin Med 2015; 4(6): 1325-47
3. Butler D et al. Nature 2008; 453: 840-842
4. Editorial. "Repetitive flaws". Nature 2016; 529: 256

Symposium 35

Renal fibrosis: new insights

Monday, 17.00 – 18.30, HALL E



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CHANTAL KOPECKY
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HDL quality is impaired in chronic kidney disease

Compositional changes in CKD increase CVD risk

unsatisfactory efficacy of lipid-targeted therapies in renal patients may be that distinct differences in lipid profiles exist between the CKD and non-CKD population. Kidney patients develop complex abnormalities in lipid and lipoprotein regulation, which become more pronounced with advancing renal failure. Particularly lipoprotein metabolism, which is a highly dynamic process, displays massive impairments, not merely affecting lipid concentrations but also involving particle maturation, composition and biological activities.

A prominent marker of uremic lipid disturbances is impaired high-density lipoprotein (HDL) quality. Among those alterations of HDL in the course of CKD are both reduced levels of HDL cholesterol and reduced functional activity strongly affecting the atheroprotective capacity of the molecule. Systemic and metabolic disturbances present in CKD patients result in a further alterations of HDL functionality and can even convert the particles into deleterious molecules. Recently, HDL quality has been assessed extensively in patients with renal failure, demonstrating a characteristic and disease-specific HDL phenotype, represented by a substantial impairment of its atheroprotective properties, affecting cholesterol efflux, antioxidative and antiinflammatory activity or endothelial functions. Additionally, the proteomic composition of uremic HDL is profoundly altered with distinct enrichment of specific proteins such as serum amyloid A (SAA), associated with systemic inflammation or surfactant protein B (SP-B) related to pulmonary congestion (Figure 1). Importantly, we

found that incorporation of SAA into uremic HDL is directly responsible for the impaired antiinflammatory properties [1].

Addressing the question if impaired HDL quality may be reversible with recovery of renal function, we could demonstrate a profound remodeling of HDL from kidney transplant recipients, together with dysfunctional cardioprotective properties, such as decreased cholesterol efflux capacity and diminished antioxidative activity. The persistent alterations of HDL quality after transplantation indicate a direct pathological role of HDLs potentially contributing to the substantial cardiovascular risk in this population [2]. Hence, CKD-associated HDL dysfunctions have several adverse consequences associated with cardiovascular complications, and the focus of current investigation is addressing the specific biologic and molecular features of HDL quality. As emerging evidence points toward a combination of structural and functional aspects of HDL responsible for its atheroprotective mechanisms, it may prove beneficial to extend measures of HDL beyond functional assays such as cholesterol efflux capacity. Another key metric of HDL quality related to cardiovascular risk and events, is the distribution and amount of HDL proteins. The concept of quantifying HDL protein cargo has emerged by recent mass spectrometry studies which demonstrated that HDL carries a number of diverse proteins involved in several biologic functions. These proteomic analyses have greatly advanced our understanding of the complexity of HDL, as well as identified links between certain

Cardiovascular disease (CVD) is the main cause of premature death in patients with chronic kidney disease (CKD). While it is well established that advanced CKD stages, particularly end-stage renal disease (ESRD), are associated with an excessive risk of cardiovascular morbidity and mortality, patients with earlier CKD stages also already experience a substantial rate of fatal and non-fatal cardiovascular events. Pathophysiologic links between CVD and CKD include a high prevalence of traditional and non-traditional risk factors, such as dyslipidemia, fluid overload, inflammation or increased oxidative stress. Dyslipidemia already contributes significantly to cardiovascular death in individuals with normal renal function and thus has been a valuable therapeutic target in treating those complications. Since dyslipidemia is also a central element in uremic conditions, it accordingly has been a therapeutic target in kidney patients as well. However, a wide variation in the international recommendations for the management of lipid disturbances in CKD exists, emphasizing an urgent need for large, prospective clinical studies on the effectiveness of lipid-regulating therapeutics in these patients.

To date, standard lipid-lowering therapies, for example statin treatment, have been far less effective in CKD patients than in the non-CKD population, exemplified by the disappointing outcome of clinical trials aimed at improving cardiovascular outcome by targeting cholesterol levels. One reason for the

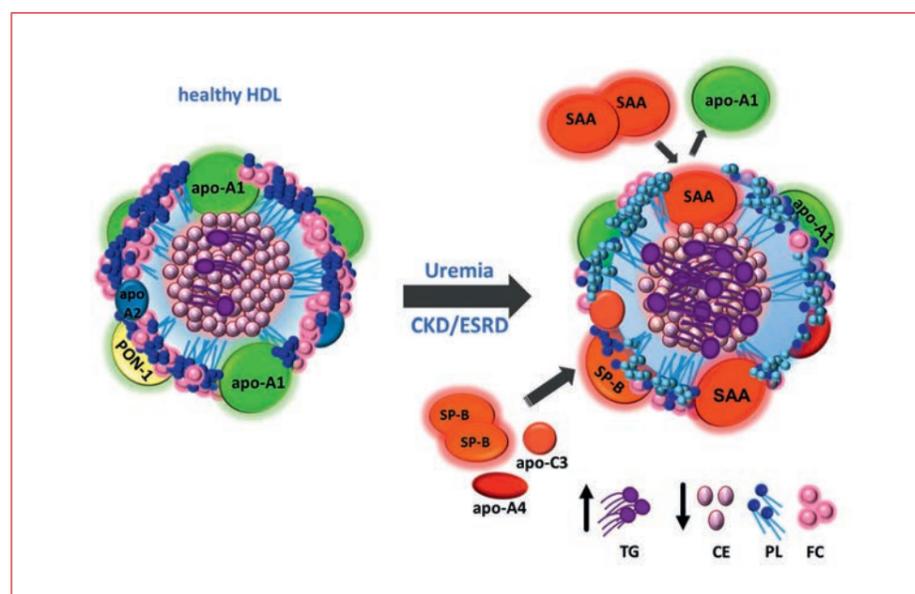


Figure 1: Schematic illustration of HDL remodeling in uremic conditions

Uremic HDL is enriched in triglycerides (TG) and various proteins such as serum amyloid A (SAA), surfactant protein B (SP-B) or apolipoprotein C3 (apo-C3), which is accompanied by loss of apolipoprotein A1 (apo-A1) and decrease in cholesterylesters (CE), phospholipid (PL) and free cholesterol (FC) content.

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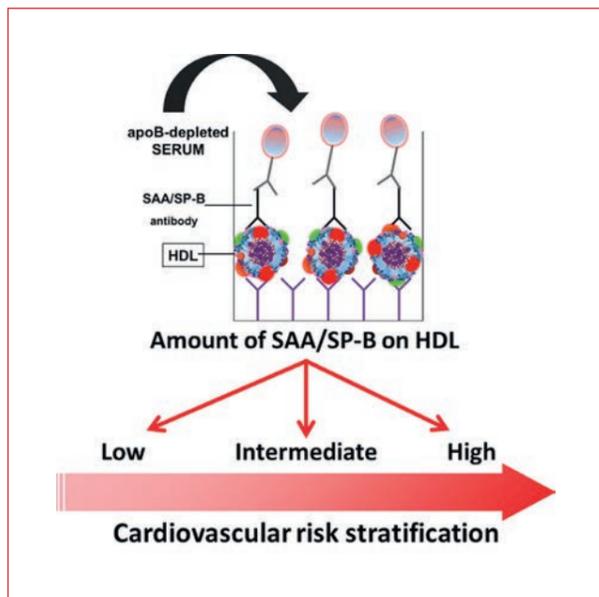


Figure 2: Novel assays for HDL functionality

Easy, robust and reproducible methods such as ELISA enable the quantification of CKD-specific HDL-bound proteins including serum amyloid A (SAA) and surfactant protein B (SP-B). Such methods will allow stratifying patients with CKD into distinct cardiovascular risk groups that may need individualized therapeutic regimens. © Saemann

structural features and the efficacy of functional properties. Intriguingly, in addition to proteins necessary for HDL to interact with the vascular wall, specific cells and other lipoproteins, assigning these to 'classical lipid metabolism', HDL

particles contain dozens of other proteins related to diverse biological actions. Many recent proteins identified on HDL, for example, are involved in complement regulation, proteolysis or the acute-phase response, indicating an essential role for HDL in inflammatory and immune processes.

At present, there is a strong need to identify and determine both functional as well as structural features of HDL in different disease populations, especially with regard to establish certain metrics of HDL quality as a diagnostic and therapeutic target. Importantly, such tools could provide a promising approach to interpret potential HDL-targeted therapies. In such an effort, we developed a novel assay to quantify HDL-bound proteins directly from serum and could demonstrate that SAA and SP-B on HDL are significant predictors for cardiac events and all-cause mortality in diabetic patients on hemodialysis, independent of HDL cholesterol levels. This strongly supports the hypothesis that dysfunctional HDL translates into clinical events and that measuring specific HDL proteins may be used as surrogates for HDL functionality [3]. However, to evaluate the full potential of HDL protein quantification for adverse clinical outcomes in renal failure as well as other high-risk populations, additional studies are necessary to link HDL-bound proteins with cardiovascular risk association. Such markers might also prove to be useful in earlier stages of CKD to assess the risk of disease progression.

In conclusion, recent evidence points towards markedly altered HDL profiles of the molecular composition and demonstrate a profound impairment of key cardioprotective

functions in different kidney disease populations. These characteristic alterations of HDL quality might be a critical molecular mechanism underlying the high cardiovascular mortality in CKD. Thus, identification of novel markers reflecting HDL functionality may have the potential to offer optimized sensitivity and specificity enhancing predictability of relevant clinical events, and they may prove valuable in redefining current prediction tools for different high-risk populations, including the different stages of renal failure. Moreover, identification and establishment of novel biomarkers does not necessarily result in replacement of conventional risk factors, but could help to improve risk prediction by augmenting established risk factors markers, thus enabling optimal cardiovascular risk estimation for individual patients (Figure 2). ■

References

1. Weichhart T et al. J Am Soc Nephrol 2012; 23(5): 934-47
2. Kopecky C et al. J Am Soc Nephrol 2015; 26(3): 565-75
3. Kopecky C et al. Clin J Am Soc Nephrol 2015; 10(2): 224-31

Symposium 36

Lipids in nephrology

Monday, 17.00 – 18.30, HALL F

Lipid lowering in CKD: yes, no, maybe

How can the guidelines help with our decision making?

The Kidney Disease Improving Global Outcome (KDIGO) guidelines [1] and the European Renal Best Practice guidelines [2] on lipid lowering in CKD share common elements, advising treatment with a statin or statin/ezetimibe combination for all adults aged ≥ 50 years with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5). This recommendation is grade 1A, which tells us that most patients should receive the recommended course of action, and the guideline groups are confident that the true effect lies close to that of the estimate of the effect. To summarize the situation for patients not on dialysis, the treatment recommendation based on evidence is telling us a YES for lipid lowering in CKD.

When patients progress to end-stage kidney disease and transition into renal replacement therapy (RRT), lipid-lowering treatment with a statin or a statin/ezetimibe combination should be continued. There are no data or a 'stopping statins' trial that provide guidance how to proceed. However, the SHARP study encourages patients to remain on treatment. If the patient has progressed to dialysis and has not been treated with a statin, treatment should not be started in patients with type 2 diabetes or in those > 50 years of age (grade 2A recommendation). Apparently the guidelines distinguish between stages of CKD (3a-5 versus 5D) and provide a NO for patients new to dialysis without prior lipid-lowering treatment.

Maybe is a word of uncertainty and does not provide clear guidance or what is expected from guidelines. However, Maybe can be translated to evidence grading level 2C or 2D. Whereas 2 (we suggest) tells us that "The majority of people in your situation would want the recommended course of action, but many would not", grade C or D quality of evidence (low or very low) is telling us that "The true effect may be substantially different from the estimate of the effect" (grade C), or "The estimate of effect is very uncertain, and often will be far

from the truth" (grade D). Quality of evidence is more a guidance than a guideline and the individual experience of the doctor in front of a specific patient may modify the procedure.

All other adults aged > 50 years with CKD and eGFR > 60 ml/min/1.73 m² (categories G1 and G2) should be treated with a statin, similar to the approach in the general population (grade 1B). In all patients after kidney transplantation treatment is also recommended (evidence level 2B), when grade B indicates moderate quality of evidence where "The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different". In patients after kidney transplantation specific statins and specific doses of statins are recommended owing to the metabolic pathways and interaction (avoid cytochrome P450 3A4 subunit and prefer fluvastatin—the ALERT Study)

We are far from having implemented the Grade 1A recommendation to provide statin or statin/ezetimibe treatment for most CKD patients in stages 3-5. A recent analysis from a large cohort in Germany (the German Chronic Kidney Disease cohort study [GCKD]) told us that implementation of the KDIGO guideline on lipid management requires a substantial increase in statin prescription rates. Approximately 50% of the cohort and a total of 707 patients with type 2 diabetes mellitus and nephropathy (an extremely high-risk group) had no statin treatment prescribed [3]. Half of these patients had a low-density lipoprotein (LDL) cholesterol > 130 mg/dl, a value that should be substantially lower according to international guidelines (the European Society of Cardiology 2012 guidelines). The reasons behind this gap may be multiple and may include not only the choices of the doctor but also of the patient, the side effects of treatment and polypharmacy. Details need to be worked out in future investigations.

Overall, KDIGO guidelines prefer the 'fire and forget' approach and are not yet prepared to 'treat to target'. The



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guidelines are based on risk assessment and treat high-risk patients. Maximum doses of statins should be avoided due to occasional side effects and a risk-benefit analysis must be done by the individual nephrologist for patients with stages 2-5 CKD and not yet having received a kidney transplant. ■

References

1. Kidney Disease Improving Global Outcome (KDIGO) clinical practice guideline for lipid management in chronic kidney disease. Kidney Int 2014; 86: 1244-52
2. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR < 45 mL/min). Nephrol Dial Transplant 2015; Suppl 2: ii1-142
3. Schneider MP et al. Kidney Int 2015; 88: 1411-18

Symposium 36

Lipids in nephrology

Monday, 17.00 – 18.30, HALL F



VLADIMÍR TESAR
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Biologic treatment was in fact first used in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) as early as the early 1990s, with the use of intravenous immunoglobulins and alemtuzumab in a small number of patients with severe AAV refractory to the standard treatment with cyclophosphamide. Although since then intravenous immunoglobulins have almost been abandoned, a recent retrospective French study demonstrated their efficacy and safety in a subgroup of patients with AAV.

Early small studies suggested the potential efficacy of anti-TNF treatment (infliximab or adalimumab) in AAV. WGET, a large US study, was, however, unable to demonstrate any efficacy for etanercept given as add-on maintenance treatment to patients with granulomatosis with polyangiitis (formerly Wegener's granulomatosis). Moreover, there was a higher number of solid malignancies in etanercept-treated patients. Anti-TNF treatment is currently neither being used nor tested in AAV.

The gradual successful introduction of rituximab for both induction and maintenance treatment of AAV is based on positive results of several randomized controlled trials (RAVE, RITUXVAS and MAINRITSAN). These completely changed our approach to the treatment of AAV, and currently rituximab is used as an equipotent alternative to cyclophosphamide in newly diagnosed patients with AAV and is preferred to cyclophosphamide in relapsing pts with AAV. Rituximab is more effective than azathioprine as a maintenance treatment of AAV and could be probably preferred in patients treated with rituximab induction.

Use of rituximab as a first-line treatment of newly diagnosed AAV still remains controversial, but it gives young patients with AAV the chance to completely avoid cyclophosphamide-related gonadotoxicity. Another area of uncertainty is the use of rituximab in patients with severe renal vasculitis. Although some data suggest that, even in these patients, rituximab and cyclophosphamide may be similarly effective, there are some concerns related to the rapidity of response



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A kidney transplant from a living donor is the best treatment for end-stage renal disease (ESRD). We owe it to all donors to perform studies on short- and long-term risks, both to ensure the safety of donors and to be able to communicate possible risks. Early studies found an increased long-term survival in donors. This would imply a survival benefit from removing a kidney. In these studies, donors were compared with the gen-

Biologic treatment for ANCA-associated renal vasculitis

Major attention is being directed towards minimizing corticosteroid

to rituximab and it is still not clear whether rituximab should be combined in these patients with short course (for example, 2 pulses) of cyclophosphamide. Moreover, it is necessary to stress that even patients treated with rituximab maintenance for 2 years may relapse after rituximab withdrawal, although their relapse rate seems to be lower than in rituximab-naïve patients. Despite the limited data available, rituximab may be restarted in these patients; the length of the second maintenance treatment remains uncertain, but should be probably prolonged.

With the ever-increasing use of rituximab in AAV patients we must also be aware of the risks of treatment. These are usually mild infusion reactions and infectious complications that are no more frequent and severe than in other patients treated with other immunosuppressive drugs. However, there are also very rare, but severe complications, such as progressive multifocal leukoencephalopathy, thrombotic events, serum sickness and pulmonary fibrosis.

In our study we were able to demonstrate that in patients with AAV who were in apparent cyclophosphamide-induced clinical remission, infiltration of the kidney with B-cells completely disappeared on rebiopsy, but infiltration of the renal interstitium with T-cells persisted. In biopsies of patients recruited for the RITUXVAS trial, T-cell interstitial infiltration and T-cell tubulitis predicted the renal outcome. One would wonder if B-cell-targeted treatment as with rituximab might effectively deplete T-cells from the kidney.

Alemtuzumab, an anti-CD52 monoclonal antibody that also depletes T-cells, was used for the first time more than 25 years ago by Martin Lockwood and David Jayne in Cambridge. Recently the same group was able to demonstrate very good long-term efficacy and acceptable safety of alemtuzumab in lower doses than used in the past in patients with AAV refractory to other treatment. Although we definitely need more data, alemtuzumab may remain a reasonable option for patients refractory or intolerant to rituximab.

Eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg-Strauss syndrome) is characterized by late-onset asthma, eosinophilia and vasculitis. Mepolizumab (an anti-IL-5 antibody) was shown to be effective in hypereosinophilic syndrome, refractory asthma and corticosteroid-dependent asthma, and is currently also being tested in EGPA where it could serve at least as a steroid-sparing

drug. Another option to mitigate asthma in these patients could be the use of anti-IgE monoclonal antibodies, such as omalizumab.

The great expectations that we could avoid most serious adverse events by replacing cyclophosphamide with rituximab were, unfortunately, not fully substantiated; for example, in the RAVE trial comparing rituximab and cyclophosphamide as induction treatment of new or relapsing AAV, adverse events were similarly frequent in both arms of the study. It becomes more and more apparent that we need to avoid the chronic toxicity of corticosteroid treatment. As well as the already mentioned options in EGPA, a very promising approach could be to interfere with the activation of the complement system.

It has been demonstrated that complement is activated in AAV through the alternative pathway and (in experimental studies) complement depletion, or more specifically interference with the C5a receptor, could completely abrogate the development of glomerular necroses and crescents. In the CLEAR study, to be presented as a poster during this ERA-EDTA Congress, remission of AAV could be induced with much lower doses of corticosteroids by using the orally active C5a receptor inhibitor CCX168. Definitely these data must be confirmed in a phase 3 trial, but minimizing corticosteroid use in AAV could mean a significant breakthrough.

In conclusion, the use of rituximab both as an induction and maintenance treatment of AAV is now well established, and rituximab is now used in increasing proportion of patients with AAV. Alemtuzumab could represent a reasonable alternative for patients with AAV refractory not only to standard treatment, but also to rituximab. Currently, major attention is directed to minimizing corticosteroid exposure. Mepolizumab in EGPA and the C5a receptor inhibitor CCX168 in AAV could be the first, but hopefully not the last, options, although their exact place in our armamentarium to defeat AAV is to be further explored. ■

Symposium 40
Kidney in systemic inflammatory diseases
Tuesday, 08.00 – 09.30, HALL F

‘Normal for now’ or ‘at future risk’?

We owe it to all living kidney donors to study their long-term risks

eral population. This comparison is not valid since donors are healthy at the time of donation, and the general background population includes everyone, including those with cardiovascular disease, cancer, diabetes and even kidney disease. It is important that studies on kidney donors include controls that are healthy enough to donate a kidney themselves. Donors are relatively young, with a mean age of around 40 years in most studies, and potential adverse effects of donation are likely to be small. Consequently, studies evaluating potential increased risks of death and ESRD in donors should have a long followup time to be able to detect possible impact on donor lifespan.

We published a study in 2014 that found increased risks for all-cause mortality, cardiovascular mortality and ESRD in kidney donors. The risk of all-cause mortality was 1.30 (95% CI 1.11-1.52) for donors compared with controls, with a corre-

sponding increase in cardiovascular death. The relative risk of ESRD was greatly increased at 11.38 (4.37-29.6). The study included 1901 kidney donors with a median age of 46 years, and a median follow-up time of 15.1 years. A paper by Muzaale et al published in JAMA in 2014 found around an 8-10 times increased risk of ESRD in those who had donated a kidney. This paper included 96,217 kidney donors, who donated a kidney in the time period 1994-2011. Median follow-up was 7.6 years.

Since recent studies have found increased risks associated with kidney donation, the interpretation of these risks in relation to clinical practice is important. In light of what is known from the general population and from studies in kidney donors, different donors will have different long-term risks of ESRD based on baseline age, sex, race or the occurrence of isolated medical abnormalities. Such an abnormality could be

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We sincerely hope you can join us in what promises to be a very productive
and impactful meeting.

Monday, May 23rd, 2016 **13:30 - 15:00**

Hall N - Level 1

13:45 Chairman's welcome

Prof. Rainer Oberbauer, Vienna

13:50 Cystinosis vs CKD: Growth and neurocognitive development in childhood

Dieter Haffner, Hannover

14:05 Managing the Adolescent Patient

Larissa Kerecuk, Birmingham

14:20 Cystinosis in Adults ; An Emerging Population

Albane Brodin-Sartorius, Paris

14:30 Discussion

14:40 Closing remarks

Lunch boxes will be provided

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mild hypertension, low-normal renal function, microalbuminuria, nephrourolithiasis, impaired glucose tolerance or obesity.

There are several aspects to consider when evaluating long-term risk. Many of these aspects have been described in several publications by Robert Steiner. Firstly, the potential donor's lifetime risk at baseline must be considered. Secondly, the incremental risk incurred by donor nephrectomy should be taken into consideration. Diseases that may be contracted later in life, such as diabetes, hypertension or primary kidney disease, may worsen remaining renal function and lead to symptomatic renal disease at an earlier age than in a similar individual with two kidneys. Reduced renal function in the donor may be a risk factor for other diseases, most importantly cardiovascular disease. This association is known from studies in chronic kidney disease populations. However, there is still some uncertainty regarding the degree to which these findings are relevant for kidney donors.

Many diseases relevant to donors develop after the fifth or sixth decades. Accordingly, a normal donor evaluation is more reassuring in an older donor than in a younger donor. Since older people in general tend to have more diseases than younger individuals, an older donor with a normal evaluation is relatively healthier than a similar younger donor. Many conditions such as diabetes or hypertension have yet to occur in a younger donor. Finally, a younger donor will spend more remaining years with only one kidney. When evaluating long-term risks

based on these facts, one may infer that remaining cumulative lifetime risk is higher in a healthy 25-year-old male than in a 60-year-old, otherwise healthy male with mild hypertension. Likewise, basic demographic factors of age and sex may have more impact on baseline risk than the occurrence of isolated medical abnormalities; for example, mild hypertension.

Presenting the risks to potential donors could be performed by providing rough estimates of absolute baseline risks and absolute risk increases. Many authors emphasize the importance of absolute instead of relative risks. This is especially important for the outcome of ESRD, since this is a rare outcome. In an individual with a low baseline lifetime risk, such as a middle-aged, healthy white female donor, even a high relative risk would be converted into a small absolute risk increase due to the rarity of the outcome. Some have stated that the low absolute risk increase should be viewed as reassuring for prospective donors. However, in those donors where remaining lifetime risk of ESRD is increased, for example a young, overweight black male with a projected lifetime risk of ESRD at baseline as high as 2-3%, a relative risk of approximately ten would not seem reassuring. If the donor were to develop kidney disease later in life, the need for dialysis would arise a few years earlier than with two kidneys.

Whether hereditary factors affect the magnitude of risk is uncertain. Most studies have only included 20-30% of unrelated donors in the study population, precluding subgroup

analyses. However, in the study by Muzaale et al, the risks of ESRD were similar for unrelated donors.

In light of results from recent studies on long-term risks in kidney donors, we have changed the written information to potential donors to include that donation may be associated with increased risks, and that these could partly be explained by genetic relationships. Furthermore, we have changed donor criteria to allow for more risk factors in older donors. We now allow older donors with microalbuminuria, mild hypertension and slight obesity, and adjust the threshold for measured glomerular filtration rate according to donor age. Hopefully, in the future we will have available more long-term data to guide information to and selection of donors. ■

References

1. Mjøen G et al. *Kidney Int* 2014; 86(1): 162-7
2. Muzaale AD et al. *JAMA* 2014; 311(6): 579-86
3. Steiner RW. *Am J Transplant* 2010; 10(4): 737-41

Symposium 38

The living kidney donor

Tuesday, 08.00 – 09.30, HALL D



MARCIN ADAMCZAK
Katowice, Poland

In women with chronic kidney disease (CKD), infertility is often observed. Such disturbance is most frequently present in females with CKD stage 5. In hemodialyzed women aged less than 40 years, primary ovarian insufficiency is more common than in the general population. In these women menopause occurs 4.5 years earlier than in healthy women. Pregnancy is rare in hemodialyzed females: prevalence is 0.3/100-females/year, which is 40 times lower than in general population. Fertility disturbances in CKD females may be caused by sexual function disorders, endocrine abnormalities leading to irregular, usually anovulatory menstrual cycles and, as we recently showed, impaired ovarian function (i.e. reduced ovarian reserve).

Disorders of sexual function are frequently observed in CKD females. Among women on chronic hemodialysis, 60-70% suffer from sexual dysfunction. More than half of such women complain of decreased libido and reduced ability to reach orgasm, with the consequent marked decline in the frequency of sexual intercourse. Pathogenesis of sexual dysfunction in women with CKD is complex and may be a result of both organic and psychological factors. Among the organic causes several conditions may be involved, including the uremic milieu per se, peripheral neuropathy, anemia, cardiovascular disease, hormonal disturbance affecting pituitary-gonadal function, and side effects of antihypertensive or antidepressant agents. Among psychological causes of sexual dysfunction in women with CKD, coexistence of depression should be underlined. Disturbances in the function of many endocrine glands (among others, the pituitary and ovaries) are common in CKD patients and their etiology is complex. Such disturbances may be caused by impaired production, secretion or metabolism of hormones by dysfunctional kidneys. Pi-

Why can't I get pregnant, doctor?

Female infertility in CKD and the role of anti-Müllerian hormone

tuitary hormone abnormalities occur early in the course of CKD and tend to increase with CKD progression. In CKD patients, the lack of appropriate cyclic release of gonadotropin-releasing hormone (GnRH) by the hypothalamus with decreased amplitude of GnRH secretory bursts is present. The aforementioned disturbances originate from hyperprolactinemia and increased serum GnRH and luteinizing hormone (LH), concentrations caused mainly by diminished renal clearances of these hormones. Abnormalities in GnRH secretion lead to a loss of typical pulsatile LH secretion by the pituitary gland. Premenopausal CKD female patients present normal, or slightly elevated basal serum LH concentration, but the pre-ovulatory rise in serum LH concentration is absent. This results in ovulation impairment.

Serum prolactin (PRL) concentration is raised in CKD females. Hyperprolactinemia found in female CKD patients is mostly caused by the increase in PRL secretion (caused by inadequate dopaminergic inhibition) and by reduced renal PRL clearance. Prolactin retention leads to inhibition of GnRH pulsatile secretion. Such hormonal abnormalities are the main causes of irregular, usually anovulatory menstrual cycles and concomitant infertility in CKD female patients. Endocrine function of ovaries in CKD females is also disturbed. In these patients serum estradiol concentration may be either normal or decreased, while serum progesterone concentration is decreased in the luteal half of the menstrual cycle. The cause of fertility disturbances in CKD females is – besides the above-described disorders of sexual function and abnormalities of pituitary-gonadal hormone secretion – impaired ovarian function; i.e. reduction in ovarian reserve. The ovaries are prone to injury by many factors because of the limited number of germinal cells and their inability to regen-

erate. The term 'ovarian reserve' refers to the remaining endowment of resting and primary ovarian follicles and is used to define the quantity and quality of follicles present in the ovaries at a given time.

Anti-Müllerian hormone (AMH) is a 140 kDa dimeric glycoprotein synthesized by the granulosa cells surrounding each oocyte in primary, preantral and small antral follicles until they reach the diameter of 6-8 mm. The rapid reduction of AMH expression is observed in larger follicles as the follicle becomes dominant. The main physiologic functions of AMH are the inhibition of excessive recruitment of primordial follicles and inhibition of preantral and antral follicular growth. This results in dominant follicle selection in the follicular phase of the menstrual cycle. The number of resting primordial follicle that are left in the ovary determines ovarian reserve.

Serum AMH concentration is proportional to the number of growing follicles and reflects the pool of primordial follicles, and therefore AMH is considered to be a marker of ovarian reserve. The highest serum AMH concentrations are observed after puberty (in 25-year-old females). Serum AMH concentration decreases with age at a rate of 6% per year until finally it is virtually undetectable in postmenopausal woman. This is related to the decrease of the quantity of growing follicles. A decrease of serum AMH concentration may indicate both physiologic and premature aging of the gonads. Recently, we have demonstrated that serum AMH concentration is significantly lower in hemodialyzed women with regular menstrual cycles than in age-matched healthy females. This may suggest that reduction of AMH secretion by the damaged granulosa cells and a reduction of ovarian reserve are the leading causes of fertility disturbances in CKD patients. Therefore infertility in CKD female patients may be partially caused by damage to the ovaries by uremic toxins.

Results of several clinical observations suggest that successful kidney transplantation improves, but does not normalize, fertility. Pregnancy is four times more common in woman after kidney transplantation than in hemodialyzed women, but it is still about 10 times rarer than in the general population. Kidney transplantation usually improves sexual func-

Fertility disturbances in females with chronic kidney disease may be caused by:

- sexual function disorders
- endocrine abnormalities leading to irregular menstrual cycles
- impaired ovarian function (reduced ovarian reserve)



FRANCESCA MALLAMACI
Reggio Calabria, Italy

The dream of every transplant physician is to be able to harvest a kidney for whoever needs it, and even more compelling is the dream that transplanted kidneys should hopefully last for the entire life of the recipient. After renal transplantation, the risk of death and cardiovascular (CV) complications such as myocardial infarction, which are highly frequent in dialysis patients, becomes less prominent and renal recipients have a significant survival advantage over those remaining on the waiting list. This advantage is due to improved renal function that slows or halts the progression of CV disease, but notwithstanding these achievements in renal transplantation, renal transplant recipients are sadly not risk free.

Indeed, almost 50% of deaths in renal transplant patients are due to CV complications, and hypertension is one of the most important CV risk factors in this patient population. Moreover, high blood pressure (BP) is a major risk factor for graft loss in this high-risk category of patients, and return to dialysis due to graft loss is the most frequent diagnosis in incident dialysis patients and a concerning economic burden for health systems worldwide. On the other hand, hypertension is a modifiable risk factor and for this reason it represents a major area of intervention for cardiovascular and renal risk reduction in kidney transplant patients.

The diagnosis and treatment of hypertension in kidney transplant patients is considered of paramount importance by current guidelines, which strongly recommend frequent BP measurements by conventional office BP. Moreover, hypertension is present in nearly all transplant recipients and fre-

tion, reduces menstrual cycle disturbances and normalize sex hormone secretion, which leads to normal Graafian follicle maturation, ovulation and luteinization. Recently, we have shown that female patients after kidney transplantation are characterized by significantly lower serum AMH concentration than healthy females, which means that kidney transplantation does not improve the ovarian reserve. Therefore, fertility disturbances, which to some extent persist after kidney transplantation, may be caused by impaired ovarian function. AMH is a protein hormone and probably like other protein hormones is cleared by kidney. This explains the observed reduction in serum AMH concentration that accompanies improvement of kidney function after successful kidney transplantation. Such hypothesis, however, needs to be confirmed in cross-sectional studies among patients at different CKD stages and in experimental animal studies.

In summary, results of our recent study suggest that fertility disturbances in CKD patients are partially caused by irreversible damage to the ovaries by uremic toxins. However, the role of serum AMH measurement as a marker of fertility prognosis in females with CKD needs further prospective clinical studies. ■

Symposium 44

New aspects of sex hormones abnormalities in CKD patients
Tuesday, 10.45 – 12.15, HALL E

Lifting the nocturnal BP burden

24-hour ambulatory blood pressure monitoring in renal transplant patients

quently complicates the medical management of these patients. The reason why hypertension is so common in renal transplantation is due to many causes and, among them, immunosuppressive drugs that help to control rejection of the transplanted kidney play an important role.

Hypertension is often resistant to therapy in renal transplant patients and multiple combinations of antihypertensive drugs, such as calcium channel blockers (CCBs), diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and diuretics are mandatory to control BP levels. However, it is worth noting that BP can be assessed not only during a consultation—the so-called 'office BP'—but also by 24-hour ambulatory BP monitoring (ABPM). This latter method is considered the gold standard for the assessment of hypertension because it provides detailed information on the circadian BP profile and separate estimates of average daytime and nighttime BP that could also be of relevance in renal transplant patients. Indeed, the lack of a fall in BP during the night or even overt high levels of BP is a recognized CV risk factor in the general population, in hypertensives and in other high-risk populations such as chronic kidney disease (CKD) patients, though the nocturnal burden of BP has been little investigated in renal transplant patients.

In a recent series in this population, the proportion of patients with a non-dipper pattern and/or nocturnal hypertension was higher than in CKD patients with comparable renal function, suggesting that confirmation of hypertension by ABPM may be an appropriate diagnostic undertaking in the renal transplant population. In renal transplant patients, the prevalence of nocturnal hypertension by far exceeds the prevalence of hypertension as assessed by clinic and daytime BP, and average 24-hour ABPM and nighttime systolic BP (SBP) and the night-day SBP ratio, but no other BP metrics, are independently associated with atherosclerosis in this population [1]. This finding is of importance because carotid intima-media thickness (IMT) is an intermediate phenotype of atherosclerosis and a powerful predictor of CV diseases, in-

cluding coronary and cerebrovascular disease. Thus, BP during nighttime may provide unique information for the assessment of CV risk attributable to BP burden in renal transplant patients.

Another important finding is the association between sleep apnea, a breathing disorder that is frequent in dialysis patients, and nighttime hypertension. Sleep apnea is mostly reversed by successful renal transplantation [2-3], and in stable transplant patients sleep disordered breathing is the most powerful functional correlate of nocturnal BP and altered BP dipping during nighttime.

In conclusion, 24 h ABPM is a formidable tool for risk assessment in kidney transplant patients and it reveals the high occurrence of nocturnal hypertension, which exceeds the prevalence of daytime hypertension and of clinic hypertension in this high-risk population. Nighttime systolic BP and the night / day ratio are independently associated with atherosclerosis. Sleep apnea is strongly associated with nocturnal hypertension. BP during nighttime may provide unique information for the assessment of cardiovascular risk attributable to BP burden in renal transplant patients. ■

References

1. Mallamaci F et al. Transplantation 2015 Dec 17. [Epub ahead of print].
2. Auckley DH et al. Am J Kidney Dis 1999; 34: 739–744
3. Mallamaci F et al. Am J Transplant 2009; 9(6): 1373-81

Symposium 43

Improving cardiovascular risk assessment in transplant patients
Tuesday, 10.45 – 12.15, HALL D

Renal Consequences of Bariatric Surgery – The Downsides

Bariatric surgery is the most effective weight reduction method available for the more than 600 million obese persons worldwide. In recent years it has become increasingly apparent that bariatric surgery can also induce regression or remission of difficult-to-treat disease states such as type 2 diabetes and may even improve longevity. Based on preliminary data there is also growing interest in the consideration of bariatric surgery as a treatment option for diabetic kidney disease and obesity-associated chronic kidney disease (CKD).

Yet while bariatric surgery offers the potential for renoprotection in addition to its proven weight reduction effects, any decision to recommend bariatric surgery must consider the risks to kidney health. One major concern is that of perioperative acute kidney injury (AKI). The first large study examining this issue reported a 9% rate of AKI within the first three days after bariatric surgery. In this study AKI was as-



ALLON FRIEDMAN
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sociated with a statistically higher rate of hospital stay (2.1 vs 1.2 days, $p=0.003$) and mortality (4.8 vs. 0%, $p<0.007$). A similar rate of AKI (during the first 30 days after surgery) was observed in a subsequent analysis of 1191 bariatric surgery patients with relatively normal baseline kidney function.

Perhaps the most widely publicized kidney-related complication of bariatric surgery is the development of kidney stones, particularly calcium oxalate stones, a phenomenon more commonly experienced after "malabsorptive" (usually defined as biliopancreatic diversion with duodenal switch or Roux-en-Y gastric bypass) surgical procedures. The disproportionate rate of oxalate-based stone formation is thought to arise from saponification of calcium in the small intestine due to fat malabsorption leading to less calcium available to bind oxalate and subsequently greater oxalate intestinal absorption. An additional factor may involve re- (continued on page 14)

(continued from page 13) duced bile salt reabsorption thus increasing its colonic concentration and leading via a direct effect to increased oxalate permeability in the colonic mucosa. In one retrospective analysis of 762 US bariatric surgery patients, new onset stone formation occurred in 11% of individuals by post-operative year six, with rates being higher (>20%) in the subgroup that underwent malabsorptive surgery. In this study calcium oxalate stones were by far the most common (94%) type observed. Of note, the authors also reported a statistically significant increase of new onset CKD over 10 years in the patients who underwent malabsorptive surgery compared to the restrictive surgery group and controls. This could at least in part be explained by another bariatric surgery-related complication, that of oxalate

nephropathy. Oxalate nephropathy involves the renal tubular deposition of calcium oxalate leading to chronic tubular injury, interstitial fibrosis, and progressive CKD and possibly end-stage renal disease. The incidence of oxalate nephropathy is not known but studies such as this and others suggest it is an underreported complication of bariatric surgery.

Finally, based on the generally recognized higher incidence of surgical complications in patients with CKD, it should be reasonably presumed that patients with preexisting CKD are also likely to have higher rates of perioperative complications or mortality after bariatric surgery than those quoted for the general population. However, data are currently lacking to quantify these risks in CKD patients. Additionally, sec-

ondary hyperparathyroidism is commonly seen after bariatric surgery and is presumed related to calcium and vitamin D malabsorption. It is therefore essential that patients with CKD and preexisting secondary hyperparathyroidism receive adequate follow-up and appropriate dietary supplementation. ■

Symposium 45

Obesity and fat tissue – what is new and what is relevant for nephrologists?

Tuesday, 10.45 – 12.15, HALL F



PETER STENVINKEL
Stockholm, Sweden

Obesity – a disease with many etiologies disguised in the same oversized phenotype

We are experiencing a global pandemic of obesity and metabolic syndrome, which has major implications for chronic kidney disease (CKD). Accurate prevention and treatment of obesity in the general population may be one of the most important action points for health officials in order to prevent the increase of CKD. Like any chronic disease affecting a large part of the population, the pathophysiology of obesity is complex and includes a combination of genetic predisposition, environment and behavioural changes. Evolution has led to metabolic thrift in humans – and when modern day humans are exposed to energy-dense food in the setting of a sedentary lifestyle, this predisposes to obesity. There is no doubt that what we eat is the single most important and modifiable determinant of human health. We recently showed that too much red meat may increase your biological age. Energy-dense food and drinks are considered to be

a major cause of obesity and type-2 diabetes. However, the current paradigm that overeating of easily digestible carbohydrates and the resulting energy imbalance as the cause of obesity has been challenged. It has been suggested instead that the host response to different nutrients contributes to overeating and obesity and that a much more complex sum of coexisting alterations, including altered neurotransmitter activity, changes in the epigenome, gut microbiota, adenovirus infection and metabolic changes triggered by specific nutrients may cause overweight (Figure 1). Thus, many different etiologies may end up in a similar obese phenotype. Whereas some nutrients promote insulin resistance and fat accumulation, other nutrients, such as antioxidants, plant food, probiotics and nuts counteract the negative effects of a calorie-rich diet by salutary effects on mitochondrial health, new dietary targets for obesity management may emerge. Although most of us would concur that eating too few calories is not the cause, but rather a symptom, of anorexia nervosa it is still believed that eating fewer calories will be a 'silver bullet' for the global obesity epidemic. Since eating disorders may be linked to altered neurotrans-

mitter system function, overeating could be a symptom rather than the cause of obesity.

Given the reported disconnection between hypercalorism, insulin resistance and overweight, the effects of different nutrients on insulin sensitivity and fat storage need attention. Many view sugar or other fructose-containing compounds, sucrose and high-fructose corn syrup as 'empty' calories. As fructose intake does not elicit an increase in glucose and insulin levels, its potential for weight gain has been regarded as negligible. However, the marked increase in fructose intake since the launching of high-fructose corn syrup in the early 1970s has paralleled the rise in BMI in USA. In contrast to glucose, fructose is not important for biochemical reactions and we can manage without it. Fructose intake induces all the features of the metabolic syndrome, irrespective of excessive energy, and promotes intracellular ATP depletion, leptin resistance, blocks satiety signals and reduces resting energy expenditure. Fructose metabolites also drive excessive food consumption by stimulation of dopamine and influence the reward system in the brain. Thus, in many ways fructose imitates the effect of its (continued on page 16)

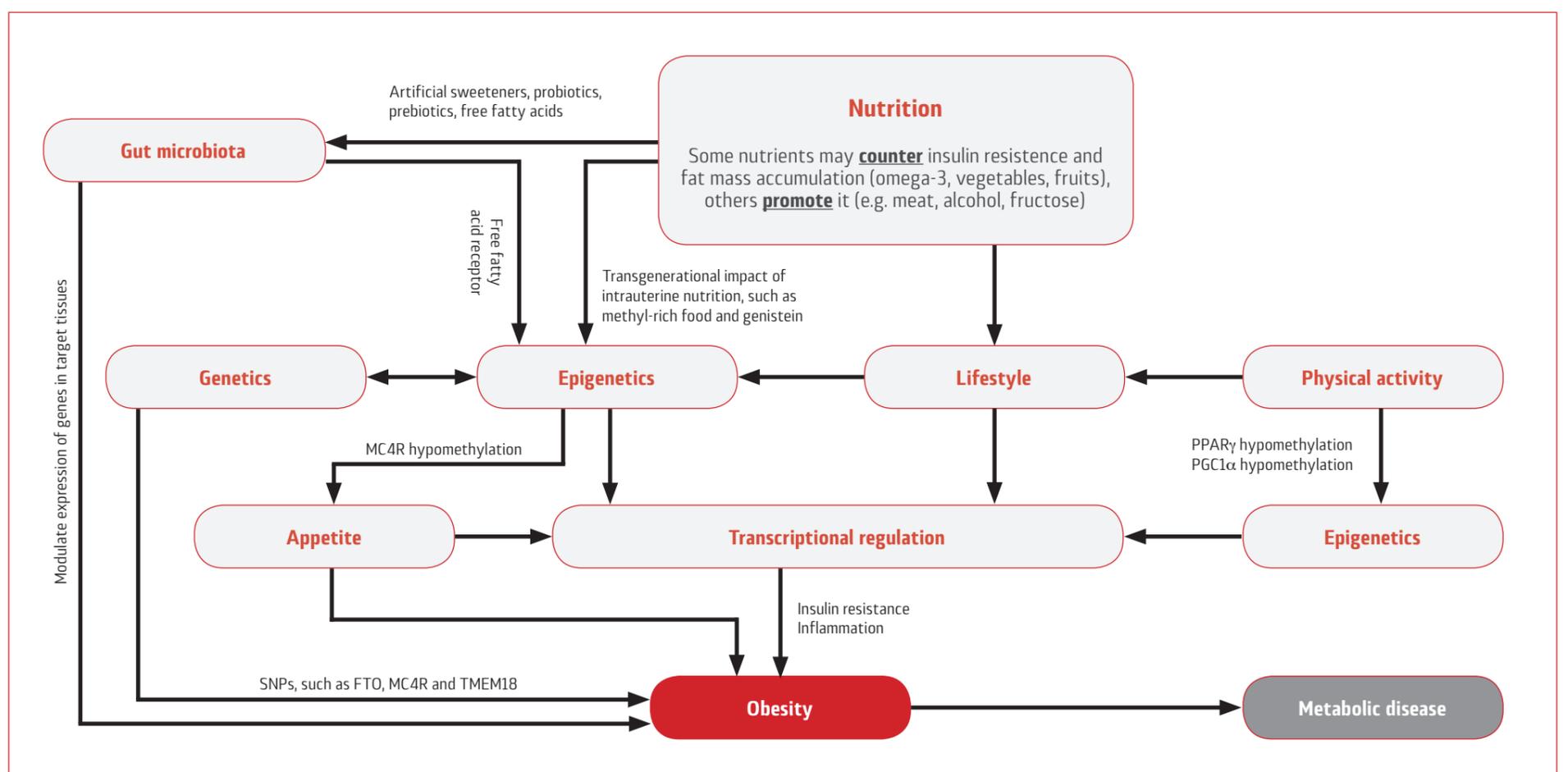


Figure 1: Figure adapted from [2]



KRZYSZTOF KIRYLIK
New York, USA

Genetic determination in IgA nephropathy

Research is pointing the way to personalized treatment approaches

Since its original description in 1968, IgA nephropathy (IgAN) has been recognized as the most common form of primary glomerulonephritis. Recent years have brought remarkable progress in our understanding of this mysterious disease, largely as a direct result of increased collaborative efforts across many research institutions in Europe, Asia, and North America. These collaborations enabled the execution of well-powered clinical and genetic studies of high quality and unprecedented size. Some of the landmark developments include the discovery of new genetic susceptibility loci, formulation of the multihit pathogenesis model, and introduction of the Oxford pathology scoring system, which represents the first evidence-based pathology scoring system in the history of this disease.

Genome-wide association studies (GWAS) have been particularly fruitful in providing novel insights into the pathogenesis of IgAN, reshaping our understanding of this disease. From a genetic viewpoint, IgAN has a complex architecture with contributions from both common and rare risk alleles, along with their genetic and environmental interactions. Although genetic contributions have been appreciated for several decades, no specific genetic factors for IgAN have been conclusively identified until the GWAS era. Because GWAS is less sensitive to genetic heterogeneity when compared to traditional linkage approaches, this study design is particularly well suited for complex traits. Nevertheless, GWAS is limited to the detection of common alleles, which typically have small effects and tend to explain only a relatively small proportion of trait heritability. Alternative strategies, such as linkage analysis combined with next-generation sequencing, are needed to discover rare variants that likely underlie the familial forms of IgAN. Such studies are presently ongoing.

Strong ethnic differences in susceptibility to IgAN have also been described, and our studies suggest that these differences likely have a genetic basis. Notably, there is a clear West-to-East prevalence gradient, with the disease being relatively infrequent in Africa, of intermediate frequency in Europe, and most common in East Asia. Similar trends are observed when the incidence of end-stage renal disease (ESRD) due to IgAN is compared between ethnicities within the United States: Asian Americans have a 4-fold higher ESRD incidence due to IgAN compared to European Americans, and a 7-fold higher incidence compared to African Americans. Additionally, a subtle South-to-North prevalence gradient has also been described within Europe, with Northern Europeans having up to 2.4-fold increased risk compared to Southern Europeans. Interestingly, the concerted pattern of interpopulation allelic differentiation across all GWAS loci parallels these prevalence patterns. Moreover, the distribution of GWAS risk alleles is strongly correlated with variation in endemic pathogens, especially with local diversity of helminthic species infesting humans. These data strongly suggest that multilocus adaptation to local infections might have shaped the present-day landscape of IgAN. Additional evidence for host-pathogen interactions shaping the genetic architecture of IgAN comes from the observation that most GWAS risk loci discovered to date encode genes involved in the maintenance of the intestinal epithelial barrier and/or are involved in response to mucosal pathogens. These loci highlight several pathways as central to the pathogenesis of IgAN, including antigen processing and presentation (MHC region), the complement system (CFHR1 / 3 and ITGAM-ITGAX loci), regulation of mucosal

IgA production (TNFSF13 and LIF / OSM loci), and innate immunity against pathogens (DEFA, CARD9, ITGAM-ITGAX and VAV3 loci). Systematic gene enrichment analyses pointed specifically to the 'intestinal immune network for IgA production' as one of the key pathogenic pathways, providing several novel targets for potential therapeutic interventions. New insights arising from GWAS contributed to the refinement of the multihit pathogenesis model for IgA nephropathy. This model, originally proposed by our group in 2011, integrates findings from the studies of galactose-deficient IgA1 (Gd-IgA1), antiglycan response, formation and deposition of IgA1-containing immune complexes, and immune complex-mediated kidney tissue injury. Abnormalities in the production of IgA1, leading to elevated levels of Gd-IgA1, represent the first hit in the model. This is likely due to dysregulation of IgA1 production at mucosal surfaces and alterations in post-translational modification of O-glycans within IgA1-producing cells. The high heritability of circulating Gd-IgA1 argues for a critical role of inherited factors in this process. Several GWAS loci appear to modulate mucosal immunity and production of IgA1 and are likely involved in the determination of this hit. However, family-based studies also demonstrate that an elevated level of Gd-IgA1 alone is not sufficient to produce IgAN and additional factors are required to trigger the formation of pathogenic immune complexes.

More recent work suggests that elevated Gd-IgA1 elicits an autoimmune response, resulting in the generation of antiglycan antibodies that recognize terminal N-acetylgalactosamine on Gd-IgA1. This antiglycan response may represent a second hit in the model, and may be incited by exposure to infectious or dietary antigens in the setting of permissive MHC-II haplotypes and favorable genetic variants in the antigen-processing pathway. The elevation of both Gd-IgA1 and antiglycan antibodies leads to formation of immune complexes (Hit 3 in the model), which then deposit in the glomerular mesangium. This deposition activates the complement pathway, stimulates mesangial cells, and induces secretion of cytokines, chemokines, and extracellular matrix proteins resulting in inflammation and fibrosis (Hit 4 in the model). Interestingly, GWAS point to the critical role of the alternative pathway activation in IgA nephropathy, which is inhibited by Factor H, but can be exacerbated in the presence of competitive Factor H antagonists, such as Factor H related protein 1 (encoded by CFHR1). GWAS have demonstrated that individuals who inherit a common deletion of CFHR1 and CFHR3 (CFHR3,1Δ) have a lower concentration of FHR1, and are protected from overactivation of the complement system by immune complexes in kidney tissue. Several studies have now confirmed that the inherited CFHR3,1Δ polymorphism is protective against IgAN.

For many of the other genetic loci, the specific causal variants are still not known. Fine mapping studies or resequencing of risk loci in large cohorts can help to identify culprit genes and potentially explain a larger proportion of disease risk. The discovery of rare variants with large effect that underlie familial forms of IgAN would also be valuable, because such variants readily demonstrate the consequence of severe gain or loss of function, and can inform the therapeutic potential of encoded gene products.

In this respect, genetic studies of pediatric patients may be especially fruitful, since affected children are more likely to be enriched for Mendelian mutations. Moreover, early onset of disease has been strongly correlated with higher burden of GWAS risk alleles. The newly established collaborative GIGA-kids Network (www.gigakids.org) that aims to enroll over 1,000 children with IgAN and HSPN for genome sequencing may be particularly well suited for new genetic discoveries. This network, initially established in North America, has re-

cently expanded to several European centers (also known as GIGA-Europe), and new recruitment sites still have an opportunity to join this effort. In addition, for both pediatric and adult patients, there is an ongoing prospective multicenter cohort study of 2,400 patients with primary glomerulonephritis (CureGN Study, www.curegn.org) that will generate data on the natural history of IgAN and provide means for a prospective validation of any new genetic findings.

In summary, GWAS provided several candidate genes for each of the hits in the pathogenesis model, but these candidates now require further followup studies. Notably, GWAS findings have already stimulated interest in several new treatment approaches, such as budesonide (a non-systemic glucocorticoid that suppresses local gut inflammation), bortezomib (proteasome inhibitor), blisibimod (BAFF inhibitor), and atacicept (APRIL and BAFF inhibitor). Follow-up studies of the molecular mechanisms underlying the risk alleles will be critical to effectively translate genetic findings into clinical applications. The ongoing human genetic and mechanistic studies aimed at refining the genetic architecture of IgAN are likely to define additional disease biomarkers and potential therapeutic targets. These efforts will be critical to enable the development of personalized treatment approaches for IgA nephropathy. ■

Symposium 50

What precipitates IgAN and what is the target for treatment?

Tuesday, 13.15 – 14.45, HALL F

Today's Highlights

Plenary Lecture 2

10.45 – 11.30, HALL A

Is it time for one-person trials? – Nicholas J. Schork, La Jolla, U.S.A.

SYMPOSIUM 27

11.45 – 13.15, HALL E

Joint Symposium ERA-EDTA & CSN (Chinese Society of Nephrology)

SYMPOSIUM 30

15.15 – 16.45, HALL D

Joint Symposium ERA-EDTA & JSN (Japanese Society of Nephrology)

SYMPOSIUM 33

17.00 – 18.30, HALL A

The Dialysis Outcomes and Practice Patterns Study (DOPPS) Program: Celebrating 20 Years and Looking Ahead

(continued from page 14) metabolic cousin ethanol, another non-essential energy source. Fructose-mediated generation of uric acid promotes obesity, fatty liver and insulin resistance; hyperuricemia precedes obesity, insulin resistance and hypertension. As lowering of uric acid has beneficial effects on the metabolic syndrome, studies that explore if low-fructose and low-purine diets reduce weight and decrease cardiovascular risk should be encouraged.

Evidence suggests that it may be possible to counteract obesity and associated metabolic disorders by inducing thermogenesis via dietary bioactive anti-oxidant and anti-inflammatory compounds. Thus, induction of mitochondrial oxidative capacity may be key for a lean phenotype. Plant phenols, a large group of metabolites that include tannins, flavonoids (anthocyanins and flavonols) and stilbenoids may antagonise insulin resistance and fat deposition. Polyphenols lower triglycerides and body weight by increasing energy expenditure, increasing fat utilisation and modulating glucose homeostasis. As resveratrol has beneficial effects on energy metabolism and mitochondrial oxidative capacity, this 'caloric restriction mimetic' may be a novel treatment for obese and insulin-resistant individuals. Lingonberries also have pronounced anti-obesity effects and prevented the metabolic effects of a high-fat diet in mice. Although nuts are rich in fat and calories, they do not increase body weight and have beneficial effects (especially walnuts) on the cardiometabolic profile. The nuclear transcription factor Nrf2 is a key activator of antioxidant genes. Thus, it can be anticipated that a low intake of nutrients rich in Nrf2 stimulators, such as polyphenols, resveratrol, allicins, lycopene and caffeine could increase the risk of obesity. Since fish-eaters have lower BMI than meat-eaters, the impact of marine lipids on insulin resistance and fat accumulation also deserves attention. The nutritional value of our food is influenced by the gut microbiota, which may play a part in the development of obesity via several mechanisms. These include increased gut permeability, metabolic

endotoxemia and the production of short-chain fatty acids, which protect against diet-induced obesity. The switch from a low-fat, plant polysaccharide-rich diet to a high-sucrose and high-fat diet produces a rapid shift in the microbiota in mice. A study of twins discordant for obesity showed that fat mass and obesity-associated metabolic phenotype were transmissible to mice with fecal cultures, elegantly demonstrating the importance of the gut microflora for overweight. This was corroborated by a study of wild hibernating bear, which showed that transplantation of summer (but not winter) bear microbiota to germ-free mice promoted adiposity without impairing glucose tolerance. It has also been shown that specific personal and microbiome features enable accurate glucose response prediction to different diets. Moreover, non-caloric artificial sweeteners, such as saccharin, sucralose and aspartame induce glucose intolerance by changing the gut microbiota towards a composition known to be associated with metabolic disease. With better understanding of the ability of both probiotics and antibiotics to harvest energy from the host gut, new dietary treatments for obesity may emerge that target the microbiome. Taken together, dietary interventions that consider the specific metabolic effects of nutrients may have a better chance of decreasing weight than putting all the focus on traditional hypocaloric diets in the treatment of obesity.

Although gross obesity is associated with significantly higher all-cause mortality in the general population, a meta-analysis showed that being obese in the range between 30-35 kg/m² was not associated with higher mortality, and that overweight (BMI 25-30 kg/m²) was actually associated with significantly lower all-cause mortality. BMI showed a U-shaped association with clinical outcomes in CKD patients also; the best outcomes were observed in overweight and mildly obese patients. Various studies have shown that high BMI is associated with better outcomes in dialysis patients. Although residual confounding by protein energy wasting, inflammation

and competing mortality risk factors may explain this paradoxical phenomenon, at least in part, it should be appreciated that in the uremic milieu, obesity may correlate with better haemodynamic tolerance and stem-cell mobilisation and with more efficient disposal of lipophilic uremic toxins. The 'obesity paradox' is observed not only in end-stage renal disease, but also in many other chronic weakening disorders associated with persistent inflammation, such as congestive heart failure, rheumatoid arthritis, coronary heart disease, cancer and diabetes. Thus, inflammation may be an important confounder of the 'obesity paradox'. A recent study of almost 6000 predominantly European haemodialysis patients showed that, whereas high BMI had a protective function and was linked to longer survival rates in chronically inflamed dialysis patients, no such defensive effect of high BMI was found in un-inflamed dialysis patients. As the correlations remained strong even after controlling for a large number of non-modifiable and modifiable factors, said study implies that overweight dialysis patients with chronic inflammation should not be recommended to lose weight. ■

References

1. Stenvinkel P et al. J Am Soc Nephrol 2013; 24: 1727-36
2. Stenvinkel P. Nephrol Dial Transplant 2015; 30: 1656-64
3. Stenvinkel P et al. J Am Soc Nephrol 2015 Nov [Epub ahead of print]
4. McClelland R et al. Aging 2016 [Epub ahead of print]

Symposium 45

Obesity and fat tissue – what is new and what is relevant for nephrologists?

Tuesday, 10.45 – 12.15, HALL F



ROSANNA COPPO
Turin, Italy

The intestine-renal connection in IgA nephropathy

In IgAN, a dysregulated mucosal immune system with defective handling of commonly encountered pathogens or alimentary components has been considered as a key triggering factor. Most of the interest, particularly in Asia, was focused on the possibility of modulating the mucosal immune system by tonsillectomy, a simple way of eradicating a source of pathogens, meanwhile reducing the MALT, but results are still inconclusive. More than tonsillar mucosa, recent evidence suggest that the intestinal mucosal immune system may play a key role in triggering IgAN (1).

The role of alimentary antigens was reported in a mouse model of IgAN by Emancipator et al. (2), and we were able to induce IgA deposits in experimental mice after gluten-rich diet in comparison to controls on gluten-free diet (3). A pilot uncontrolled study we performed in 1986 showed that gluten-free diet induced a decrease in anti-gliadin IgA, IgA containing immune complexes and proteinuria (4). However, no RCT was performed, and results showing the strong effects of renin-angiotensin blockade or corticosteroid therapy in this disease, as reported in following years, diverted interest to an easier approach than the tedious gluten-free diet.

30 years after these reports, gluten sensitivity was made a focus of scientific interest again by Smerud et al. (5), who reported on IgAN patients with a high immune response of intestinal mucosa to gluten or soy, indicating a subclinical inflammation to gluten in 30% of the patients investigated. Based on these observations, and supposing that this intestinal inflammatory condition could

represent the origin of IgA which eventually deposits in the mesangium, this group performed a pilot study investigating, in patients with IgAN, the effect on proteinuria levels of a new enteric formulation of the locally acting glucocorticoid budesonide (Nefecon®), designed to release the drug in the ileocecal region (6). Budesonide given for 6 months reduced proteinuria by 23% (by 30% after two months of additional follow-up) in patients with IgAN, indicating the interest for an RCT. The NEFIGAN phase 2b trial (ClinicalTrials.gov Identifier: NCT01738035) has just been completed and it is of interest that the primary endpoint of reduction in proteinuria after 9 months of treatment was met at interim analysis. We look forward to seeing the full analysis from this study.

The role of gliadin has also been supported recently in some interesting experimental results. Monteiro's group has reported an interaction between degalactosylated IgA1 and the myeloid receptor FcαR1 (CD89), which has been detected in renal deposits of patients with IgAN (7). In an experimental mouse strain expressing human CD89 and human IgA1, they demonstrated that the development of IgAN needs the interaction of IgA1-sCD89 with the receptor for transferrin (TfR1/CD71) and with the crosslinking enzyme transglutaminase 2. Transglutaminase 2 is an autoantigen for coeliac disease patients, and the reaction leads to villous atrophy. Papista et al. have recently reported results of a gluten-free diet in double transgenic mice that express human IgA1 and CD89 and which spontaneously develop IgAN (8). Mice on a gluten-free diet for 3 gener- (continued on page 18)

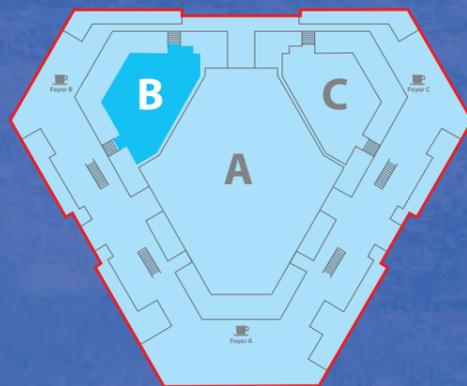
IgA nephropathy (IgAN) is the commonest primary glomerular disease worldwide and leads to end-stage renal disease in 20-40% of patients within 25 years. In spite of a large number of studies, its pathogenesis is only partially defined, and the triggering event is still to be identified. The involvement of mucosal immunity has been considered since description of the disease, following the clinical association between gross hematuria and mucosal infections, usually involving the upper-respiratory airways and sometimes the gastro-intestinal tract as well. Since IgA is the most prevalent immunoglobulin in mucosal secretions, the first hypothesis for the pathogenesis of IgAN was of a hyperactive immune response to germs presented at mucosal surfaces. The mucosal surface of the respiratory and gastrointestinal tracts represents a 400m² interface with the environment, commensal bacteria and pathogens, alimentary components and potentially noxious substances introduced by water, aliments and air. The mucosal-associated lymphoid tissue (MALT) represents 50% of total body immunity and accounts for 70% of total antibody production, mostly in the form of secretory IgA, providing specific immunologic protection against both resident flora and infectious pathogens.

New insights into iron metabolism and deficiency



Chair: Professor Angel de Francisco
Co-Chair: Professor Kai-Uwe Eckardt

Monday 23 May 2016
13:30–15:00
Hall B, Level 2
Austria Center Vienna



Programme

- 13:30** **Lunch boxes will be provided**
- 13:45–13:50** **Chair's introduction**
Angel de Francisco (*Santander, Spain*)
- 13:50–14:10** **ID prevalence in patients with CKD – a matter of definition?**
Kai-Uwe Eckardt (*Erlangen, Germany*)
- 14:10–14:30** **Iron pathophysiology – its complexity and our knowledge gaps**
Tomas Ganz (*Los Angeles, USA*)
- 14:30–14:50** **Diagnosing and treating ID/IDA – meeting your patient's needs**
Jolanta Małyszko (*Bialystok, Poland*)
- 14:50–15:00** **Closing remarks and Q&A**
Angel de Francisco

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(continued from page 16) ations had almost no mesangial IgA deposits or renal injury. The exposure to gluten led to intestinal inflammation, IgA anti-gliadin antibodies, hematuria and proteinuria.

Although there are frequent case reports of an association between IgAN and inflammatory bowel disease, the high frequency of subclinical IgAN left open the possibility of that association being random. However, renal biopsies in cases of renal complications during inflammatory bowel disease, including Crohn's disease and ulcerative colitis, showed that IgAN was more frequent than other glomerular diseases, suggesting a causal link between the two diseases. On the other hand, 4% of patients with IgAN were found to have celiac disease, versus 0.5-1% in the general population.

Apart from gluten and other alimentary components, particular interest has recently been focused on the extraordinarily large number of microbes which are present in the gut, collectively called microbiota, which can vary according to diet and environmental factors. They are probably modulated by host genes and affect MALT activity (9). More specifically, gut microbiota control the organization and maturation of lymphoid tissues and act both locally and systemically to coordinate recruitment, differentiation and function of innate and adaptive im-

mune cells. The microbiota contributes to the immune function of MALT, e.g. by controlling the T-helper balance, and it was found to play an unsuspected role not only in inflammatory bowel disease but also in autoimmune diseases. A correlation with diet has been inferred from some recent studies, as dietary changes are known to affect both the composition and function of the gut microbiota, which in turn can modulate the innate and adaptive immune system.

A recent genome-wide association study (GWAS) of IgAN has shown interesting new associations between IgAN and loci associated with risk of inflammatory bowel disease or maintenance of intestinal barrier and intestinal MALT response to pathogens (10). All these recent data suggest a tempting new hypothesis for a strong intestine-kidney connection in IgAN (Figure 1).

In conclusion, some data suggest a new hypothesis for a strong intestine-kidney connection in IgAN. A defective immune tolerance might favor an abnormal response to microbiota with alterations of the intestinal barrier, including increased absorption of alimentary antigens and bacterial toxins, triggering MALT activation and subclinical intestinal inflammation. This can produce an abnormal response to alimentary antigens or commensal microbes with synthesis of aberrantly glycosylated polymeric IgA1,

which eventually enters the circulation with renal deposits formation. The hypothesis is also tempting because it offers new treatment options, targeted at subclinical intestinal inflammation. ■

References

1. Coppo R. Nephrol Dial Transplant. 2015;30:360-6.
2. Emancipator SN et al. J Exp Med 1983; 157: 572-582
3. Coppo R et al. Lab Invest 1989; 60: 499-506
4. Coppo R et al. N Engl J Med 1986; 315: 1167-1168
5. Smerud HK et al. Nephrol Dial Transplant 2009; 24: 2476-2481
6. Smerud HK et al. Nephrol Dial Transplant 2011; 26: 3237-3242
7. Berthelot L et al. J Exp Med 2012; 209: 793-806
8. Papista C et al. Kidney Int. 2015;88:276-85. 10.1038/ki.2015.94. Epub 2015 Mar 25. PubMed PMID: 25807036
9. Anders HJ et al. Kidney Int 2013; 83: 1010-1019
10. Kiryluk K et al. Nat Genet 2014; doi: 10.1038/ng.3118

Symposium 50

What precipitates IgAN and what is the target for treatment?

Tuesday, 13.15 - 14.45, HALL F



FRANCESCO P. CAPPUCCIO
Coventry, United Kingdom

Salt consumption and cardiovascular disease: from etiology to prevention

The evidence. Salt (i.e. sodium chloride) is causally related to blood pressure (BP). The higher the salt intake, the higher the BP, an effect seen since birth. A small and sustained reduction in salt intake (up to 50% of what we eat now) causes a fall in BP. The evidence from controlled studies, small and large, short and long, all agree on the following: (1) salt intake is one of the major determinants of BP in populations and individuals; (2) a reduction in salt intake causes a dose-dependent reduction in BP – the lower the salt the lower the BP; (3) the effect is seen in both sexes, in people of all ages and ethnic groups, and with all starting BPs. Similar results have been described in children. High BP causes strokes and heart attacks and a reduction in BP is associated with their reduction. A reduction in salt intake reduces BP, stroke and other cardiovascular events, including chronic kidney disease, by as much as 23% (i.e. 1.25M deaths worldwide). The effect is related to the size of the fall in BP, the bigger the fall in BP the greater the benefits. It is therefore conceivable that a moderate reduction in salt intake in a population would help reduce stroke, heart attacks and vascular kidney disease through BP reduction. The collective evidence from a variety of sources indicates that a lower salt intake is associated with a lower incidence of fatal and non-fatal cardiovascular disease (CVD), in particular stroke.

The preventive imperative. In a population, there is a log-linear (exponential) relationship between the levels of BP (that are normally distributed) and the risk of developing a cardiovascular event, especially stroke. Whilst the relative risk of having a stroke is highest in the upper level of BP (i.e. the hypertensives), the attributable events in the population (absolute risk) are fewer than those that would be attributable to the moderate relative risk of moderate levels of BP amongst the majority (i.e. the normotensives). There-

fore, a shift in the entire BP distribution, even of a moderate amount, would avert a greater number of events than just the 'treatment' of those at the extreme end of the BP distribution. Population salt reduction strategies aim at exactly this. In 2004, the British government, through the Food Standards Agency, started a programme of population salt reduction through media campaigns to increase public awareness and the demand for change, engagement with the food industry on a voluntary basis to set targets for sodium content in foods and to obtain reformulation of many common food categories, and repeated national surveys using 24-hr urine collections to monitor intake. Ministers also proposed legislation if the industry refused to make reductions voluntarily. As a result, salt intake in the UK fell from 9.5g per day in 2001 to 8.6g per day in 2008. In England & Wales,

the government target was set at 6g per day by 2012, sadly remaining higher than the target of 4g per day achieved in the US DASH trial and recommended by NICE in 2010. A reduction of 3g per day in salt intake would result in a BP fall of at least 2.5/1.4 mmHg. This would reduce strokes by approximately 12-14% and CHD by some 9-10%, approximately 6,500-8,000 stroke deaths and 7,500-12,000 CHD deaths per year. In the USA, a reduction in salt intake of 3g per day would reduce the annual number of new cases of cardiovascular disease (CVD) by approximately 10% (some 60,000-120,000 fewer CHD cases, 32,000-66,000 fewer strokes and 54,000-99,000 fewer heart attacks), reductions comparable with those projected for interventions targeting tobacco, obesity or primary prevention with statins and anti-hypertensives.

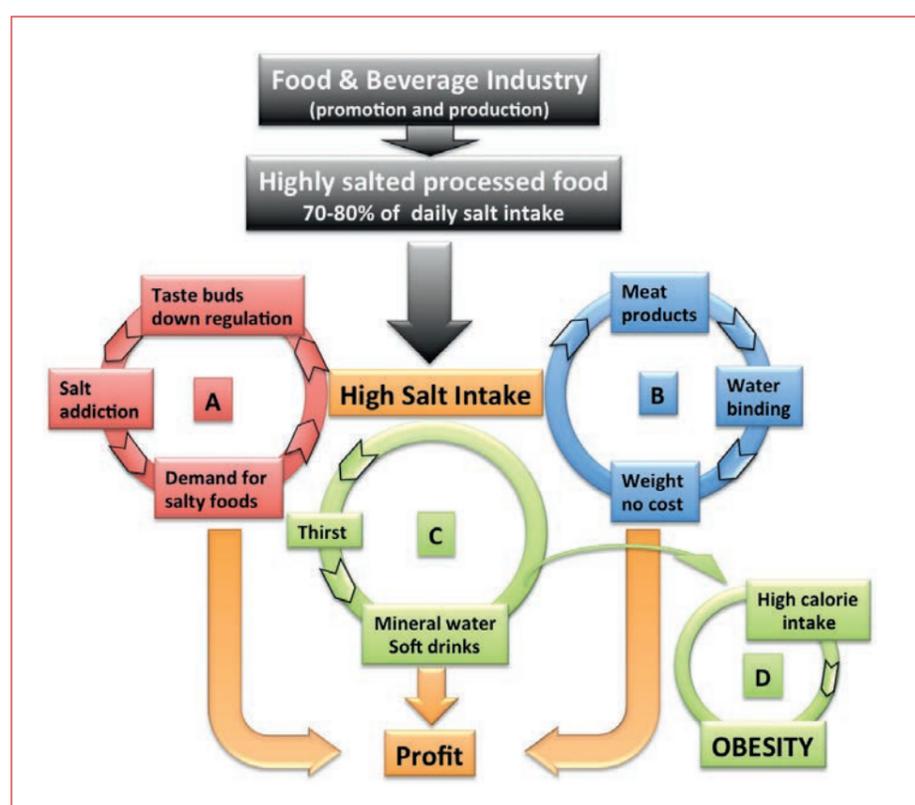


Figure 1: Cycles of Profit

© Cappuccio

The economic imperative. All countries need to satisfy stringent cost-effectiveness criteria within a general climate of ageing populations, escalating healthcare demands and recently reduced financial resources. Economic modelling studies have assessed the health effects and financial cost of reducing population salt intake. Despite methodological differences, they all demonstrate that a reduction in salt intake is cost saving. In the USA, a salt reduction of 3g per day would result in an estimated annual gain of 194,000–392,000 Quality Adjusted Life Years, a measure of added healthy life, and savings of \$10b to \$24b in health care costs, a \$6 to \$12 return on investment for each dollar spent on the regulatory programme. Even a more modest reduction of 1g per day achieved gradually over 10 years would be more cost-effective than using medications to lower BP in all patients with hypertension. These economic savings would be achieved with either voluntary or mandatory reductions in the salt content of processed foods. Health benefits would be up to 20 times greater with government legislation on salt limits in processed foods. Cost savings are also estimated for a 15% reduction in salt intake in low- and middle-income countries, which would avert 13.8M deaths over 10 years at an initial cost of less than \$0.40 (US) per person per year.

The political imperative. Since 1985, the World Health Organization (WHO) has been recommending a reduction in population salt intake to an average of 5g per day from a country's customary consumption. However, no action plan was ever put in place globally, although notable implementations in Japan and Finland led to dramatic reductions in CVD and stroke rates associated with substantial reductions in population salt intake. Over the following 20 years, both scientific evidence and public health initiatives led to renewed recommendations from the WHO in 2007 and 2012 not to exceed a population average salt intake of 5g per day. A significant step toward global policy action was the 2011 United Nations high-level meeting on non-communicable diseases (NCDs), which set a target for population salt reduction as a priority to reduce premature CVD mortality by 2025. Revised WHO guidelines now recommend a 30% reduction of salt intake by 2025 and a final maximum target of 5g per day. The latter target was then adopted as a resolution by the 66th World Health Assembly in 2013.

The controversy. This important shift in public health has not occurred without obstinate opposition from organizations primarily concerned with the profits deriving from high salt intake by the population and less with public health benefits (Figure 1). The food and beverage industry has been particularly obstructive regarding public health actions, either directly or through its public relations organizations. Its strategies have included mass media campaigns, biasing research findings, co-opting policy makers and health professionals, lobbying politicians and public officials, and encouraging voters to oppose public health regulation. Key components of this denial strategy are misinformation (with "pseudo" controversies) and the peddling of numerous rather well-worn myths. In general, poor science has been used to create uncertainty and to support inaction. An example are the analyses of prospective observational studies suggesting that lower salt intake might be associated with increased risk of CVD events, in particular coronary events and heart failure. These studies have been the object of intense scrutiny due to numerous methodological flaws that would introduce fatal biases (errors) in the results and, hence, erroneous conclusions. The errors pertain to the domains of systematic errors in the assessment of salt intake, the presence of 'reverse causality' bias, the presence of residual confounding, random errors and insufficient statistical power. It has also been argued that a randomized clinical trial would be needed to prove that a reduction of salt intake in populations over an extended period of time reduces the rate of strokes and heart attacks. However, whilst we explore the feasibility of a trial, we should not refrain from implementing public health policies based on the judicious use of the best available evidence. Never was a randomized clinical trial of (continued on page 22)

Imaging oxygen metabolism: new findings in both animal and human studies



CHRISTOFFER LAUSTSEN
Aarhus, Denmark

The introduction of hyperpolarized carbon-13 magnetic resonance imaging has enabled researchers to interrogate the metabolic conversion of endogenous substrates in vivo in real time. This novel technology allows derangements in the metabolic profile in diseases to be assessed. More importantly, it can be used as a prognostic tool for predicting the outcome of different treatments faster than current state-of-the-art techniques.

In this talk, I will focus on the use of hyperpolarized magnetic resonance to interrogate the oxygen metabolism associated with renal disease and in particular with diabetic nephropathy and ischemia reperfusion in animal models. I also wish to present the translation towards introduction in renal impaired patients.

Hyperpolarized MR relies on generating an artificially enhanced transient MR signal for a non-radioactive stable isotope biomarker prior to injection of this given biomarker. This is typically [1-13C]pyruvate, the metabolic fate of which can be used to interrogate the interplay between anaerobic and aerobic metabolism simultaneously, within seconds after injection (Figure 1). The natural abundance of carbon-13 in nat-

urally occurring pyruvate in the human body is only around 1% of all carbon atoms, and standard MR sensitivity to these carbons is inherently low. Hyperpolarized MR thus enables allows background-free images of the biomarker distribution to be obtained, very similar to positron emission tomography (PET) (Figure 2).

Hyperpolarized MR has recently been translated to human subjects, showing the ability to distinguish malignant from benign tissue in prostate cancer patients. The technique uses hyperpolarized carbon-13 pyruvate, via an elevated metabolic conversion of pyruvate to lactate via the enzyme lactate dehydrogenase (2). In this talk, I will review current knowledge concerning metabolic alterations in renal disease in animal models interrogated with hyperpolarized MR and discuss how this can be applied to humans.

References

1. Laustsen C. Front Physiol 7: 72, 2016
2. Nelson SJ et al. Science Translational Medicine 5: 198ra108, 2013

Symposium 51

Hypoxia in kidney disease: integrating pre-clinical with clinical research
Tuesday, 13.15 – 14.45, HALL B

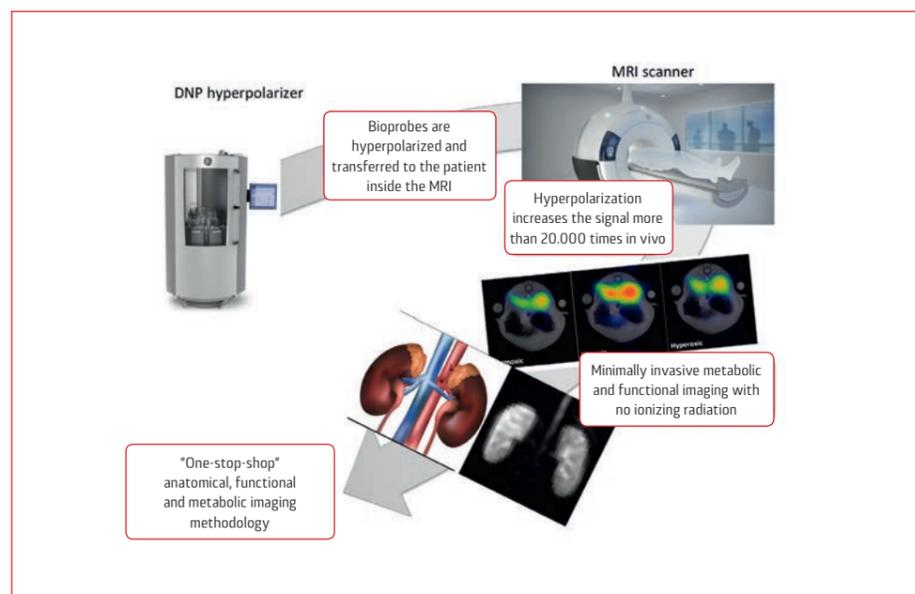


Figure 1: Dissolution dynamic nuclear polarization magnetic resonance imaging – a "one-stop-shop" methodology © Laustsen

The biomarker is hyperpolarized and transferred by intravenous injection to the patient lying in the clinical scanner. This procedure increases the sensitivity of the measurements by more than 20,000 times, and enables the direct interrogation of renal uptake and metabolic turnover. Standard clinical magnetic resonance imaging (MRI) capabilities are simultaneously available and provide a very versatile and sensitive diagnostic modality that is free of ionizing radiation and thereby ensures patient safety [1].

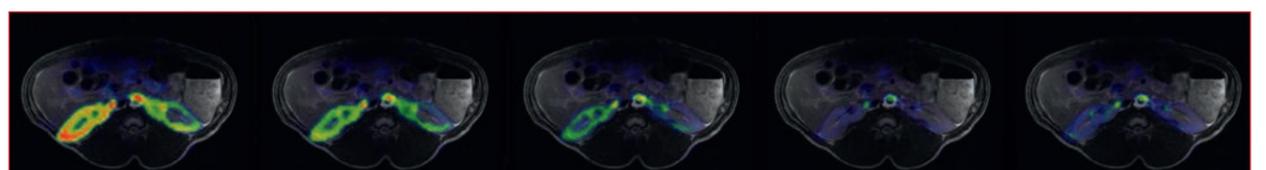


Figure 2: Hyperpolarized pyruvate renal signal distribution (overlaid the standard anatomical MR) and following decay in large animal model acquired with an advanced MR sequence allowing multiple time frames. © Laustsen



SUSAN M. OTT
Seattle, U.S.A.

Limitations of the current therapies for osteoporosis in patients with CKD

Patients with chronic kidney disease (CKD) have an increased incidence of low-trauma fractures. In those with moderate stage 3 CKD the risk is about twice that seen in patients with similar age but normal kidney function. The risks are even higher in those with late stages of CKD, and up to half of dialysis patients older than 50 will suffer from fractures.

Over the last 2 decades several new medications have been developed to treat osteoporosis. In large randomized trials, and in surveys of use in clinical practice, these drugs have been shown to substantially reduce the risk of fragility fractures of the spine, hip, and other bones. Because there is overlap between osteoporosis and mild to moderate kidney disease, these randomized trials have included some subjects with eGFR lower than 60. The osteoporotic patients with mild CKD had more fractures than those with normal GFR. Post-hoc analysis of the trial results suggest that the relative reductions in fracture rates were similar. However, it is important to realize that the eligibility for subjects in the trials was strict and those with abnormal calcium, parathyroid, or alkaline phosphatase were excluded. We can conclude that patients with early CKD, especially when the reduced GFR is due to natural aging, who have normal lab values and low bone density, can be treated with medications for osteoporosis and will have fewer fractures than if they are untreated.

The challenge for clinicians, however, is how to tell when the efficacy and safety results can be extrapolated to patients with later stages of CKD. When the PTH, calcium, and alkaline phosphatase become abnormal, the skeletal abnormalities become more complex. And, unfortunately, the clinical trial data become very sparse. Additionally, vascular calcifications develop, which are related to bone metabolism and must be considered when treating osteoporosis. Figure 1 illustrates a CKD patient with both vertebral fractures and aortic calcifications.

Bone density does not give the same information in CKD patients as in the general population. A low and decreasing bone density will nearly always be associated with decreased bone strength. However, normal or high bone density does not always mean the fracture risk is normal. Thus, studies in dialysis patients frequently do not find a relationship between bone density and fracture prevalence, or there is an increased risk of fracture when measuring cortical sites, but the strength

of the relationship is not as predictable as in postmenopausal osteoporosis. This is because the quality of the bone is not normal in CKD patients (Figure 2). Skeletal fractures depend on both the force applied to the bone (such as trauma from a fall or accident) and the bone strength, which depends on the bone quantity as well as quality.

Patients with CKD have poor muscle strength and often balance problems and these contribute to falls despite any other treatments. In a study from Canada, simple measures of muscle strength were more closely associated with fractures than the bone density. Treatment to prevent fractures should include balance and strength training.

The bone density is not the only factor related to the bone strength but it is often of major importance. When bone resorption is increased, as with hyperparathyroidism, but bone formation is unable to keep pace with resorption, there will be loss of bone tissue. This directly decreases bone strength.

Excess resorption also increases the risk of perforation of bone trabeculae, resulting in deterioration of the micro-structure of bone. Imagine sawing through every third beam of a bridge – without losing much of the metal, the bridge would collapse. These trabecular structural abnormalities can cause changes seen with high resolution imaging such as peripheral CT or MRI. Some of these studies have been able to show that poor trabecular patterns are associated with fractures in CKD patients. Medications that slow resorption can prevent some of this microarchitectural deterioration. Thus, patients on treatment may have fewer fractures than those who are untreated. The bone volume, however, is not restored because the medications currently available also reduce the bone formation. With prolonged treatment the bone quality becomes more brittle.

Density depends on both the volume of the bone and the mineralization. In CKD bone may be poorly mineralized. The most obvious is in overt osteomalacia, but even when bone appears to be mineralized on a histological section, the density of mineralization can be lower than optimal. On the other hand, if the mineralization density is too high, the bone becomes brittle. This process is familiar to paleontologists, who study fossil bones which are no bigger than the bones of the animal when it was alive, but they are certainly denser. A fracture that occurred while the dinosaur was living or just at the time of death will have a splintered appearance, whereas a fracture that occurs after the bone is fossilized has a sharp edge. Fractures with similar sharp edges are seen in patients with excessively dense bones, such as those with osteopetrosis or prolonged therapy with bisphosphonates. The min-

eralization density increases when both bone resorption and formation are severely suppressed.

Other aspects of bone quality relate to the structure of collagen, the collagen cross-linking, the size and distribution of the crystals within the bone matrix. Diseases such as osteogenesis imperfecta cause abnormal collagen, diabetes can increase glycosylation of the collagen fibrils and reduce their strength. Levels of the serum minerals (calcium, phosphorus, magnesium, and bicarbonate) can alter the crystal structure. The collagen structure and crystals are also abnormal in kidney disease. Because patients with CKD have so many abnormalities that are not usually seen in patients with ordinary osteoporosis, the treatment is more difficult and less likely to be effective. The turnover varies from extremely high to unmeasurably low. The volume is often decreased in cortical bone but may be increased in cancellous bone. Many of the regulators of mineralization are abnormal, as well as the hormones that control mineral metabolism. Furthermore, bone metabolism is linked to vascular calcification, and physicians must determine effects on both the skeleton and the vasculature.

In patients who fracture, it makes sense to optimize the known abnormalities in calcium, phosphate, and parathyroid, using recommendations that apply to all kidney patients. These have not been proven to reduce fracture risk, with the exception of using cinacalcet in elderly patients with high parathyroid levels, seen in a post-hoc analysis of the randomized trial. Raloxifene improved bone strength in animal models and slightly improves bone density in small studies of women on dialysis. It is a logical choice but without enough evidence to strongly recommend it. Bisphosphonates are the most commonly used medications in those with ordinary osteoporosis, but they suppress bone formation by over 95%. The long-term effects in ordinary osteoporosis are still uncertain but about 1 in 1000 women have atypical femur fractures after 8 years. The long-term effects on vascular calcification are unknown, but since there is an inverse correlation between calcifications and bone formation, this could potentially be a problem.

Denosumab is a newer medication that also severely suppresses bone formation, so the same concerns would apply with long-term use as with the bisphosphonates. In late stages of CKD, many patients develop severe hypocalcemia. Teriparatide, which is human PTH 1-34, is the only available anabolic agent. It increases both bone formation and resorption in patients with ordinary osteoporosis, with formation prominent. In patients with CKD who have low PTH (most of them from previous surgery), a few case reports have shown improvements in bone density. This is a logical approach that would only apply to a small number of patients.

An exciting potential new treatment in ordinary osteoporosis is antibodies to sclerostin. The early phase studies show increase in bone formation and decrease in bone resorption, with formation of good quality lamellar bone. A recent announcement suggested that fractures were reduced in a large clinical trial. In mice with CKD, blocking sclerostin was beneficial, and future studies will certainly be done to explore this approach in patients. ■

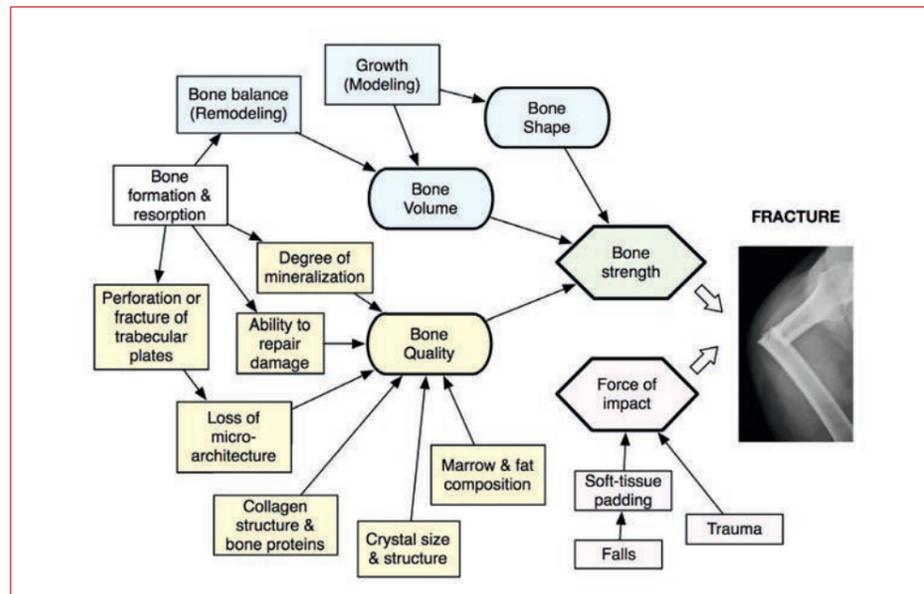


Figure 1: Bone Quality

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Figure 2: FX and Aortic Calcif

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Symposium 55
Gone with the Wnt
Tuesday, 14.45 – 16.15, HALL F

Management of Hyperkalemia: Challenges and Considerations in Patients with CKD

Invitation to a CME Symposium at the ERA-EDTA 2016 Congress, Vienna

Monday, May 23, 2016
13:30-15:00
Hall C, Level +2

Purpose of Activity

Hyperkalemia is a serious disturbance with increasing prevalence and a new treatment paradigm. Oral ion exchangers should have value not only to reduce the acute threat of hyperkalemia but also to achieve and maintain normal serum potassium levels enabling optimal use of renin-angiotensin-aldosterone system (RAAS) inhibitors for which there are proven clinical benefits. This broadens the range of eligible patients, lengthens the time on treatment and extends the focus to include the outpatient arena. Although as a general rule all instances of hyperkalemia should be deemed actionable, the nature and urgency of appropriate actions depend heavily on clinical judgment and are influenced by the initial point of care. The purpose of this presentation is to bring forward some of the considerations that inform clinical judgments essential to the evaluation and management of hyperkalemia in the outpatient CKD arena. Program content includes a review of the cellular mechanisms that normally ensure potassium homeostasis, how these are affected by RAAS inhibitors, hyperkalemic risk assessment based on clinical trials, and characteristics of the ideal, current and emerging oral ion exchangers.

Educational Objectives

After completing this activity, the participant should be better able to:

- 1: Review the mechanisms that regulate potassium balance, and how they are affected by RAAS inhibition.
- 2: Describe the pathophysiology of hyperkalemia as affected by underlying conditions that modify clinical outcomes.
- 3: Identify considerations that clarify the urgency of actionable degrees of hyperkalemia based on information from clinical trials.
- 4: Present information on emerging oral ion exchangers and how they may affect current practices.

Agenda/Faculty

- 13:30 Lunch**
- 13:45 Introduction and Questions Programme Chair**
David Goldsmith, MA, MB, BChir
Professor and Consultant Nephrologist
Renal Unit, Guy's and St Thomas' Hospital
London, UK
- 13:55 Pathophysiology and Risk of Hyperkalemia**
Johannes FE Mann, MD
Professor of Medicine
Friedrich Alexander University of Erlangen, Germany
International Scholar, Population Health Research Institute
McMaster University, Canada
- 14:15 Current and Emerging Options for Outpatient Treatment of Hyperkalemia**
Martin H. de Borst, MD, PhD
Tenure Track Assistant Professor and Consultant Nephrologist
Department of Nephrology, University Medical Center Groningen
Groningen, The Netherlands
- 14:35 Summary / Question / Assessment of Learning**
Professor David Goldsmith
- 14:45 Panel Discussion / Question and Answer Session**
All faculty led by Professor David Goldsmith
- 15:00 Closing Remarks / Meeting adjourned**
Professor David Goldsmith

PHYSICIAN ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of SynAptiv and The Med Ed Group, Inc. SynAptiv is accredited by the ACCME to provide continuing medical education for physicians. SynAptiv designates this live activity for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

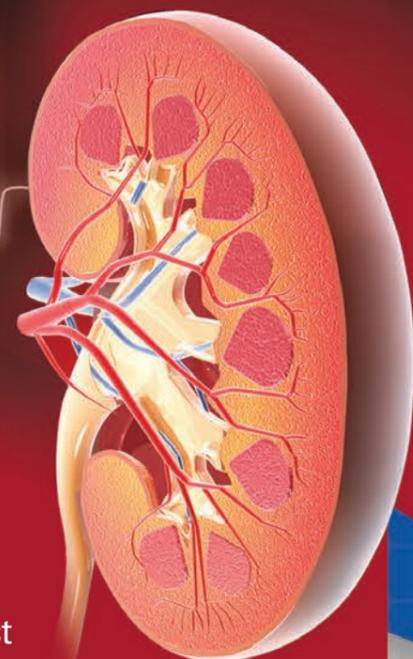
Target Audience

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

This symposium is funded by AstraZeneca



This activity is jointly provided by SynAptiv and The Med Ed Group, Inc.



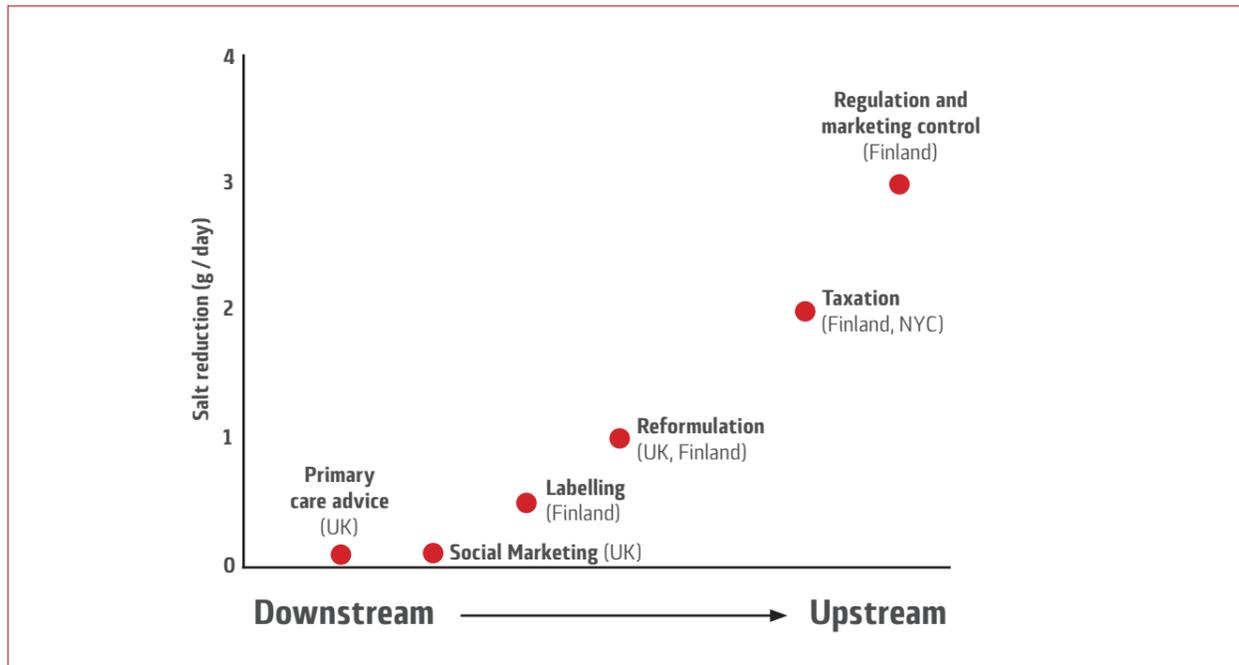


Figure 2: Hierarchical effectiveness of policy options for a population reduction in salt intake © Cappuccio

(continued from page 19) tobacco smoking and lung cancer carried out in humans to 'prove' that smoking causes lung cancer and that we should eventually ban tobacco. Furthermore, the bulk of evidence supporting population action on salt reduction dwarfs the evidence that today supports accepted policies on weight reduction, physical inactivity, and dietary intake of fibre, fruit and vegetable for the prevention of both cancer and CVD.

Policy options. A number of policy options for the implementation of national programmes globally are now available and population salt reduction is underway in many countries worldwide. In industrialized countries, most of the salt in diet is added to food during the manufacturing process (up to 75%), with only 15-20% due to consumer's choice (adding salt to food at the table or when cooking), the remainder occurring naturally in food. Hence, to achieve a re-

duction in population salt intake, a reformulation of the salt content of food is necessary in addition to the reduction of discretionary use. The UK experience indicates that, in the early stages of a salt reduction programme, it is possible to take 5-15% of the salt out of a product gradually without a noticeable change in flavour, sales, or complaints about taste. Various policy interventions are currently being tested or implemented worldwide (Figure 2) through national and international initiatives, including voluntary agreements with the food industry to reformulate, regulatory target setting for reformulation, and salt-substitution policies. From global experience, a regulatory approach is feasible and acceptable, as demonstrated in Finland, and necessary, as seen in the UK, where the involvement of industry in policymaking, in the form of the Responsibility Deal, resulted in a significant delay in progress towards salt reduction targets. ■

References

1. Aburto NJ et al. Br Med J 2013; 346: f1326
2. Cappuccio FP et al. Am J Hypertens 2014; 27(2): 279-81
3. Cappuccio FP et al. Br Med J 2011; 343: 402-5

Symposium 54
Salt on the table
Tuesday, 14.45 – 16.15, HALL E



PANTELIS A. SARAFIDIS
 Thessaloniki, Greece

Frequent or longer hemodialysis – benefits more than risks?

Data like the above indicate the presence of a strong link between day-of-week mortality and dialysis schedule and call for ways to eliminate the relevant risk through re-evaluation of timing and frequency of the prescribed hemodialysis regimens. Over the years, various patterns of frequent and/or longer, home or in-center, dialysis schemes have been implemented in various countries with the aim of offering a more continuous renal replacement therapy and minimizing the risks arising from accumulation of uremic toxins, large changes in hydration status, and fluctuations in electrolyte and acid-base parameters. Their benefits and risks are briefly summarized below.

Frequent hemodialysis

Frequent hemodialysis schemes most commonly involve short, daily hemodialysis (5-7 weekly sessions of 1.5-3 hours' duration), or nocturnal dialysis (5-7 weekly sessions of 6-8 hours) either in-center or in the home. The seminal Frequent Hemodialysis Network (FHN) trial randomized 245 patients in 6-times-weekly in-center hemodialysis or conventional thrice-weekly hemodialysis for 12 months and showed that frequent hemodialysis was associated with a significant 39% reduction in the risk of death or change in left ventricle mass index, assessed by magnetic resonance imaging, and with a 30% reduced risk of death or change in the physical-health composite score of the RAND 36-item health survey, which were the two coprimary outcomes. However, in the FHN Nocturnal Trial, which assigned 87 individuals to 6-times-weekly home nocturnal hemodialysis or 3-times-weekly conventional hemodialysis for 12 months, the frequent dialysis scheme had no effect on similar coprimary outcomes, a finding attributed to the small sample size. The main and post-hoc analyses of FHN trials and subsequent randomized studies also showed that frequent hemodialysis is superior to conventional thrice-weekly hemodialysis in a number of intermediate outcomes, such as phosphorus levels and number of phosphate binders, BP control and number of antihypertensives, arterial stiffness, total body water

composition and self-reported quality-of-life, but not on anemia, nutritional status or cognitive function. Furthermore, such studies also noted elevated risks of vascular access complications and interventions, worsened residual renal function and increased burden of therapy, resulting in higher rates of method discontinuation among patients receiving frequent dialysis, which may minimize any beneficial effects.

The controversy over the actual benefit-risk ratio of frequent dialysis is further intensified by the contradictory results of such schemes in respect of hard outcomes. An earlier retrospective study of 26,016 incident hemodialysis patients with 856,007 patient-months of follow-up during 1996-2007 in Australia and New Zealand showed no significant difference in survival between patients receiving frequent in-center hemodialysis and conventional thrice-weekly hemodialysis. A matched-cohort study including 1,873 patients receiving daily home hemodialysis and 9,365 controls receiving thrice-weekly hemodialysis selected from the USRDS database during 2005-2008, showed that daily hemodialysis was associated with a 13% lower risk of all-cause mortality. Another study examined 338 patients from the International Quotidian Dialysis Registry who received intensive home hemodialysis between 2000-2010 matched with 1,388 patients on conventional dialysis participating in the DOPPS study and showed that intensive hemodialysis is associated with a 45% reduction in the risk of all-cause mortality as compared to conventional hemodialysis during 3008 patient-years of follow-up (HR: 0.55; 95% CI: 0.34, 0.87). In contrast to all the above, a more recent retrospective cohort study revealed that during 1,382 patient-years of follow-up, 318 patients from the International Quotidian Dialysis Registry receiving short daily hemodialysis (more than 5 times per week) had a significant 60% higher risk of death than 575 matched controls receiving conventional thrice-weekly hemodialysis (HR:1.6; 95% CI 1.1-2.3).

From the start of hemodialysis as replacement therapy for end-stage renal disease (ESRD), hospital- or unit-based dialysis treatment is typically scheduled thrice weekly, due to reasons unrelated to health and disease status, but to 'calendar logistics' relevant to the weekly work schedule. Thus, hemodialysis patients under this schedule remain outside dialysis for two short intervals (~2 days) prior to the second and third weekly dialysis sessions and for a long interval (~3 days) during the weekend. However, the capacity of hemodialysis patients to maintain homeostasis of metabolic and volume parameters is equally impaired on all seven days of the week; it has therefore been hypothesized that the problematic intermittent nature of conventional hemodialysis would translate to a heightened risk of complications, particularly towards the end of the 3-day interval and the following dialysis session. Not surprisingly, large observational studies conducted in hemodialysis patients in recent years have confirmed this hypothesis, showing that the first day of the dialysis week (i.e. Monday or Tuesday), including the last hours of the long interdialytic interval and the subsequent dialysis session, is associated with increased cardiovascular morbidity and mortality compared to any other day of the week. Various mechanisms have been proposed for this increased risk towards the end of the long interval, including greater volume accumulation and blood pressure (BP) increase, larger fluctuations in electrolyte and acid-base parameters, activation of the renin-angiotensin and the sympathetic nervous systems, increase in wave reflections from the periphery, faster progression of left-ventricular hypertrophy, and others.

It is noteworthy that, due to low power, none of the actual randomized studies in the field documented superiority of frequent dialysis with regards to overall mortality and hard cardiovascular outcomes. Up to this point, important evidence derives from a very recent analysis of the FHN trial, which evaluated patient outcomes after the 12-month intervention period covering a median of 3.6 years post-randomization and showed decreased mortality of around 45% in the frequent dialysis group (HR:0.54; 95% CI: 0.31-0.93 and with censoring of time after kidney transplantation HR 0.56; 95% CI 0.32-0.99) (Chertow JASN 2015 in press). Again, this contradicts a similar analysis of the FHN Nocturnal Trial showing that in the long-run (median follow-up 3.7 years), nocturnal hemodialysis is associated with largely increased mortality (HR:3.88; 95% CI, 1.27-11.79), a fact attributed to a very low death rate in the conventional group. Overall, these data call for adequately powered future trials to fully elucidate this issue.

Extended-time hemodialysis

Another option for attenuating the mortality risk attributed to the conventional thrice-weekly dialysis regimens could be extended-time, in-center or in-home nocturnal hemodialysis; although scheduled 3 times per week, this reduces the duration of the long interdialytic period from 68 to about 60 hours. A case-control study prospectively followed 247 patients assigned to 8-hour in-center nocturnal hemodialysis and another 247 age-, sex-, diabetic status-, and dialysis duration-matched control subjects assigned to conventional thrice-weekly hemodialysis for 12 months. Extended-time nocturnal hemodialysis was associated with a 72% lower risk of all-cause mortality during follow-up than for control subjects (HR:0.28, 95% CI 0.09-0.85), along with lower hospitalization rates, regression in LVMI, decreased use of antihypertensive drugs, phosphate binders and erythropoietin, and better cogni-

tive function. A subsequent prospective study compared 746 consecutive patients who initiated extended-time, in-center, nocturnal hemodialysis and 2,062 controls on conventional thrice-weekly hemodialysis for 2 years. Nocturnal hemodialysis was associated with a 25% reduction in the risk of all-cause mortality, after adjusting for age, BMI and dialysis vintage (HR: 0.75; 95% CI: 0.61, 0.91), along with disappearance of the day-of-week effect on occurrence of mortal events, an increase in calcium, albumin, and hemoglobin, and a decrease in phosphate, and pre-dialysis BP levels.

Every-other-day hemodialysis

Every-other-day or alternate-day hemodialysis is a dialytic modality which slightly increases the dialysis frequency (i.e. 3.5 sessions per week), but eliminates the long interval which is associated with complications, and could be potentially related to lower rates of vascular access interventions, method withdrawal and technique failure compared to more frequent schemes. Preliminary observational studies suggested a beneficial effect of every-other-day dialysis on BP control and cardiovascular symptoms. The first interventional data on the effects of this modality come from a study that randomized 18 hemodialysis patients to every-other-day or conventional thrice-weekly hemodialysis for a year. Every-other-day hemodialysis produced reductions in pre-dialysis BP, left ventricle mass index and dose of erythropoietic agents. Finally, a modality that combines elements from the two aforementioned schemes is long (7-8 hours) nocturnal every-other-day dialysis; a recent crossover study randomized routine hemodialysis patients to nocturnal every-other-day hemodiafiltration of standard (20-30L) or increased (35-50L) convective volume for 6 months each and showed improvements versus baseline in BUN, creatinine, and β 2-microglobulin clearance, as well as phosphate, BP and LVH in both groups.

In summary, accumulated observational evidence indicates that the conventional thrice-weekly dialysis schedules are associated with particularly increased morbidity and mortality risk towards the end of the long interdialytic interval, a fact supported by several pathophysiologic mechanisms. Cohort and clinical studies evaluating the benefits and risks of more frequent or longer hemodialysis schemes have provided beneficial results on intermediate cardiovascular endpoints, but with possible drawbacks relevant to vascular access function and increased burden of therapy. Every-other-day hemodialysis could be a more practical solution for avoiding the 3-day interval with less of the above problems. Given the contradictory findings regarding the effects of frequent or longer dialysis on mortality, additional research efforts, including properly-designed clinical trials with hard end-points, are warranted in order to fully elucidate the benefit-to-risk ratio of these alternative dialytic modalities. ■

References

1. Foley RN et al. N Engl J Med 2011; 365: 1099-1107
2. Georgianos P et al. Am J Nephrol 2015; 41:400-408
3. Diaz-Buxo JA et al. Semin Dial 2013; 26: 578-589
4. Chertow GM et al. N Engl J Med 2010; 363: 2287-2300
5. Chertow GM et al. J Am Soc Nephrol 2015. [Epub ahead of print]

Symposium 52

Personalized dialysis

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Our mission is to improve the outcome of patients with kidney disease in a sustainable way

Interview with Prof. Wim Van Biesen, chair of European Renal Best Practice



WIM VAN BIESEN
Ghent, Belgium
Chair of European
Renal Best Practice

European Renal Best Practice (ERBP) was founded in 2008. Why was it necessary to have a European nephrology guideline initiative?

VAN BIESEN: Well, one of the major reasons, of course, is that there is exponential growth in the number of papers and studies. For an individual nephrologist or general physician, it is hard to keep track of all the publications and to form an opinion. On top of that, the quality of the published literature varies from extremely poor to extremely good. The industry also has its own interests and uses some studies for marketing. So it is not easy to evaluate all the evidence objectively and digest all the information – and that is what guideline commissions do. Another important point is that we need sustainable health care. In times of budget constraints and economic downturn, it is very important that every Euro we spend is spent efficiently. Physicians and patients will understand that we cannot spend money on a treatment that

is not working, or on treatments for which we do not know whether they work or not. Guideline commissions check the evidence of interventions and only recommend those with a proven benefit. This should assure that on the long term our health care system remains sustainable and that interventions that do work are available to all who need them.

What is the guideline philosophy of ERBP?

VAN BIESEN: Our mission is to improve the outcome of patients with kidney disease in a sustainable way. We want to be as objective as possible. We do systematic reviews of the literature, we compile and digest the data. After discussion among experts, we come up with a recommendation. This is not written in stone, but it gives nephrologists and patients a basis for their shared decision. Another important point is that ERBP is financed by ERA-EDTA and is thus fully independent of industry. I think that is very important with regard to objectivity.

Which guidelines have already been published so far?

VAN BIESEN: Well, four full guidelines have already been published – and two are in the pipeline. In 2013, we published the “ERBP Guideline on the Management and Evaluation of the Kidney Donor and Recipient” and the “Recommendations for the management of crush victims in mass disaster”, in 2014 the “Clinical practice guideline on diagnosis and treatment of hyponatraemia”, which is available in 18 different languages. Last year, the Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL / min) was issued. Apart from that,

we have published a large number of position statements and clinical advice papers on various topics. In contrast to full guidelines, these focus on one small aspect of management only, and are usually published up-to-date, when a particular issue raises concerns among experts.

Let's talk about future projects. Which ERBP guidelines are coming next?

VAN BIESEN: The next upcoming guideline concerns the **management of elderly persons with advanced kidney disease**, a population that is growing due to the demographic shift. The guideline has been divided into three parts: The first part focuses on objective medical issues, e.g. how do we measure renal function in these patients, how do we improve their functional status or predict their progression. The recommendations of this part can be found at the booth of ERBP during the conference, and are open for comments and suggestions of the ERA-EDTA membership. We hope to be able to publish the guideline in two, three month. The second part is somewhat more philosophical and societal, focusing on palliative care, the patients' dignity and life quality. In the third part, we have pro-con debates on topics where there is not a lot of evidence or even no evidence at all. Different papers in this series have meanwhile been published. Besides, we are currently working on a **guideline on vascular access**. It is a very big project, involving all the major players, such as the Vascular Access Society, the European Society for Vascular Surgery, the German vascular access society, and the RedVA project. It takes time, of course, but we are optimistic that the guideline can be published end of this year. ■



DAVIDE BOLIGNANO
Reggio Calabria, Italy

Dialysis modality choice in diabetic patients with ESKD

Still searching for a way out of the conundrum?

has shown that people with diabetes had half the odds of being recommended for PD. Such an observation was in complete opposition to another similar survey among Canadian, British and American nephrologists showing that diabetes tends to favour PD slightly.

The issue whether first dialysis choice may impact on hard clinical outcomes for diabetic patients has been specifically addressed by the European Renal Best Practice (ERBP) group as part of their recent diabetes guidelines [1]. The evidence systematically retrieved was mostly confined to observational studies assessing the mid- to short-term risk of death in PD vs. HD in incident cohorts. Results were highly inconsistent, potentially influenced by selection and lead-time bias and other methodological pitfalls and varied across study designs, follow-up period and subgroups. Although no evidence-based arguments were found in favour of or against a particular dialysis modality as first choice treatment in patients with diabetes and ESKD, some concerns seem to arise about choosing PD in elderly and frail patients, since this technique was associated with a higher risk of death, particularly within the first three years. Sparse data were obtained on the risk of infectious complications. Conversely, no information was available on the impact of dialysis modality choice on quality of life, patient satisfaction, major and minor morbid events, hospital admissions, deterioration of residual renal function, functional status, glycaemic control, access to transplantation

or survival of the technique. In the absence of targeted studies, specifically designed to clarify such an issue, modality selection in diabetic patients should still be driven by subjective preferences and individual conditions, after unbiased patient information about the various available treatment options. Making sure that all the different renal replacement therapy modalities can be made equally available for all patients is indispensable to allow free modality choice. ■

Diabetes is the most frequent cause worldwide of end-stage kidney disease (ESKD) requiring chronic renal replacement therapy. Yet the question as to what could be the optimal dialysis technique for treating diabetic patients, be it peritoneal dialysis (PD) or haemodialysis (HD), still remains unanswered. Constant exposure to glucose in the dialysate may worsen glycaemic control in diabetic patients when on PD. On the other hand, PD therapy may be better tolerated than HD because of a more stable blood pressure, particularly in subjects with overt autonomic neuropathy. No less important, the creation of a good vascular access in the presence of advanced diabetic vasculopathy may be challenging, and fistula failure episodes may become frequent. In the recent past, randomized controlled trials comparing PD to HD have been demonstrated to be very problematic due to recruitment and equipoise problems. Proper clinical guidelines are therefore limited, and there is considerable heterogeneity in practice across countries with regard to the information given to patients on the dialysis modality to be preferred as first option. A recent survey conducted in the US among nephrologists

References

1. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL / min). *Nephrol Dial Transplant* 2015; 30(Suppl 2): ii1-142

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Looking through RIFLE, AKIN and KDIGO glasses: do we see the same?

MARLIES OSTERMANN
London, United Kingdom

SYMPOSIUM 32
AKI – pathophysiology and definition
MON 15.15–16.45, HALL F



Uremic xerosis influences uremic pruritis in CKD

JACEK C. SZEBIETOWSKI
Wroclaw, Poland

SYMPOSIUM 34
Whole person care in Nephrology
MON 17.00–18.30, HALL D



The metabolic risk profile before and after renal transplantation

ADNAN SHARIF
Birmingham, United Kingdom

SYMPOSIUM 43
Improving cardiovascular risk assessment in transplant patients
TUE 10.45–12.15, HALL D



Extracorporeal treatment of immune mediated kidney disease

GEORGE S. REUSZ
Budapest, Hungary

SYMPOSIUM 53
Special technological aspects of ICU nephrology
TUE 14.45–16.15, HALL D



Is online HDF the new standard for extracorporeal therapy?

FRANCESCO LOCATELLI
Lecco, Italy

SYMPOSIUM 52
Personalized dialysis
TUE 14.45–16.15, HALL A



Sclerostin and the CV System

VINCENT BRANDENBURG
Aachen, Germany

SYMPOSIUM 55
Gone with the Wnt
TUE 14.45–16.15, HALL F

Tomorrow's Highlights

SYMPOSIUM 39

08.00 – 09.30, HALL E

Joint symposium ERA-EDTA & ESPN (European Society for Paediatric Nephrology)

Plenary Lecture 3

09.45 – 10.30, HALL A

Transplantation tolerance: can it turn into a reality? – Kathryn Wood, Oxford, United Kingdom

SYMPOSIUM 42

10.45 – 12.15, HALL A

Joint symposium ERA-EDTA & ESH (European Society of Hypertension)

SYMPOSIUM 46

10.45 – 12.15, HALL B

NDT Polar Views

SYMPOSIUM 49

13.15 – 14.45, HALL D

YNP: Tomorrow's nephrology



**MARLIES
OSTERMANN**
London, United Kingdom

Looking through RIFLE, AKIN and KDIGO glasses: do we see the same?

These important tools must be interpreted within the clinical context

Acute kidney injury (AKI) is a syndrome that affects 13-18% of patients admitted to hospital and is particularly common in patients in the intensive care unit (ICU). The impact and prognosis vary considerably depending on severity, acute and chronic comorbidities and geographical location.

The definition of AKI has evolved from the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria in 2004 to the AKI Network (AKIN) classification in 2007 (Table 1). In 2012, both were merged, resulting in the Kidney Disease Improving Global Outcomes (KDIGO) classification. The key differences are:

1. The AKIN and KDIGO classifications use a smaller change in serum creatinine to define AKI compared to the RIFLE definition.
2. The RIFLE criteria include a 7-day window, whereas the AKIN and KDIGO classification have incorporated a 48-hour window.
3. The AKI classification stipulates that adequate fluid resuscitation should have been undertaken and urinary obstruction excluded before the criteria are applied. This was not specified in the RIFLE and KDIGO classification.
4. The RIFLE definition includes glomerular filtration rate criteria and allows the use of the Modification of Diet in Renal Disease (MDRD) formula to back-calculate baseline renal function.
5. The AKIN and KDIGO classification include 'renal replacement therapy' as a separate criterion to define AKI stage 3, irrespective of serum creatinine.

Several studies have shown that all three classifications demonstrate an association between AKI and clinical outcomes. However, the incidence and stages of AKI vary when 2 or 3 classifications are applied to the same patient population.

Importantly, all 3 classifications are based on changes in serum creatinine and/or urine output. However, creatinine and urine output are markers of excretory function only and do not provide any information about any other roles of the kidney, i.e. metabolic, endocrine or immunological functions. They are also not kidney specific and may change independent of renal function. As a result, there are patients who have clear evidence of AKI but who do not meet the RIFLE, AKIN or KDIGO criteria, and there are also patients who fulfill the criteria but have not had a significant change in their renal function (Table 2). Until more sensitive and specific biomarkers are routinely used in clinical practice, it is essential to interpret changes in serum creatinine and urine output within the clinical context. Finally, AKI is a syndrome and may have numerous different etiologies. The RIFLE, AKIN and KDIGO classifications only serve to diagnose and stage AKI but do not provide any information about the underlying etiology.

In conclusion, the RIFLE, AKIN and KDIGO classifications are important tools to diagnose, stage and prognosticate AKI but need to be interpreted within the clinical context. ■

Serum creatinine criteria		Urine output criteria
RIFLE criteria		
RIFLE Risk	Creatinine rise ≥ 1.5 - to 2-fold from baseline or GFR decrease $> 25\%$	< 0.5 ml / kg / h for > 6 h
RIFLE Injury	Creatinine rise > 2 -fold to 3-fold from baseline or GFR decrease $> 50\%$	< 0.5 ml / kg / h for > 12 h
RIFLE Failure	Creatinine rise > 3 -fold from baseline or Creatinine rise ≥ 354 $\mu\text{mol/l}$ with an acute rise of ≥ 44 $\mu\text{mol/l}$ or GFR decrease $> 75\%$	< 0.3 ml / kg / h for 24 h or anuria for 12 h
RIFLE Loss	Complete loss of kidney function for > 4 weeks	
End-stage kidney disease	End-stage kidney disease > 3 months	
AKIN classification		
Definition	An abrupt (within 48 hours) reduction in kidney function defined as an absolute increase in serum creatinine of either ≥ 0.3 mg / dl (≥ 26.4 $\mu\text{mol/L}$) or an increase $\geq 50\%$ (1.5 fold) from baseline or a reduction in urine output (after exclusion of hypovolemia and obstruction).	
Stage 1	Creatinine rise by ≥ 26 $\mu\text{mol/l}$ (> 0.3 mg / dl) or Creatinine rise 1.5- to 2-fold from baseline	< 0.5 ml / kg / h for > 6 h
Stage 2	Creatinine rise 2-fold to 3-fold from baseline	< 0.5 ml / kg / h for > 12 h
Stage 3	Creatinine rise 3-fold or more from baseline or Creatinine rise to ≥ 354 $\mu\text{mol/l}$ with an acute rise of ≥ 44 $\mu\text{mol/l}$ or RRT irrespective of serum creatinine	< 0.3 ml / kg / h for 24 h or anuria for 12 h
KDIGO classification		
Definition	AKI is diagnosed if serum creatinine ≥ 26 $\mu\text{mol/l}$ over ≤ 48 hours, or rises to ≥ 1.5 -fold from baseline which is known or presumed to have occurred in the preceding 7 days.	
Stage 1	Creatinine rise ≥ 26.5 $\mu\text{mol/l}$ in 48 h or Creatinine rise 1.5-1.9 times from baseline	< 0.5 ml / kg / h for 6-12 h
Stage 2	Creatinine rise 2.0-2.9 times from baseline	< 0.5 ml / kg / h for ≥ 12 h
Stage 3	Creatinine rise 3 times from baseline, or Creatinine rise to ≥ 353.6 $\mu\text{mol/l}$ or Initiation of RRT irrespective of serum creatinine	< 0.3 ml / kg / h for ≥ 24 h or anuria for ≥ 12 h

Table 1: RIFLE, AKIN and KDIGO classifications for acute kidney injury

Abbreviations: AKIN = Acute Kidney Injury Network; GFR = glomerular filtration rate; KDIGO = Kidney Disease Improving Global Outcomes; RIFLE = acronym for Risk, Injury, Failure, Loss, End-stage; RRT = renal replacement therapy

Clinical scenario	Consequence
Administration of drugs that interfere with tubular secretion of creatinine (i.e. cimetidine, trimethoprim)	Misdiagnosis of AKI (rise in serum creatinine without change in renal function)
Reduced production of creatinine (i.e. muscle wasting, liver disease, sepsis)	Delayed or missed diagnosis of AKI
Ingestion of substances that lead to increased generation of creatinine independent of renal function (i.e. creatine)	Misdiagnosis of AKI
Obesity	Overdiagnosis of AKI if urine output criteria are applied to actual weight
Conditions associated with physiologically increased GFR (i.e. pregnancy)	Delayed diagnosis of AKI
Interference with analytical measurement of creatinine (i.e. 5-fluorocytosine, cefoxitin, bilirubin)	Misdiagnosis and delayed diagnosis of AKI (depending on the substance)
Fluid resuscitation and overload	Delayed diagnosis of AKI (dilution of serum creatinine concentration)
Hypovolemia and physiologic oliguria	Misdiagnosis of AKI

Table 2: Potential pitfalls of AKI definition based on creatinine or urine output
Abbreviations: AKI = acute kidney injury; GFR = glomerular filtration rate



**JACEK C.
SZEPIETOWSKI**
Wroclaw, Poland

Uremic xerosis influences uremic pruritis in CKD

The common clinical problems are challenging for both physicians and patients

Pruritus is defined as an unpleasant cutaneous superficial sensory sensation leading to scratching. Although this descriptive definition is an old one, proposed in 1660, it seems to be still accurate. According to the classification of the International Forum for the Study of Itch (IFSI), chronic pruritus lasts for more than 6 weeks, is usually associated with chronic diseases, is frequently difficult to control and significantly influences patients' wellbeing.

One of the six categories of chronic pruritus is dedicated to systemic causes. Uremic pruritus, also called uremic itch or more recently chronic kidney disease (CKD)-associated pruritus, is placed in the systemic itch category. It is an itch associated with CKD that is not present in acute kidney injury. Uremic pruritus is still a common clinical problem and a clinical challenge for both physicians and patients. There are several studies on the epidemiology of uremic pruritus, but sometimes they are difficult to compare due to different methodologies applied, especially in the earlier studies.

In general, uremic pruritus was extremely common in the past, especially among patients on dialysis, with a prevalence ranging up to even 85%. In the last decades of the last century, the frequency of uremic pruritus was estimated as 40-60%, and a recent representative cross-sectional German study has documented even lower incidence, with a point time prevalence of 25%. However, in our survey performed last year, almost 53% of hemodialysis patients reported uremic pruritus in the past, and 46% were affected by itch within the previous 3 days. The observed decrease in the prevalence of uremic pruritus is believed to be due to improved dialysis techniques and generally better care of this group of patients. Epidemiologic studies of uremic pruritus in the pediatric population are very rare. Recently we clearly showed that uremic itch affects about 20% of children suffering from CKD, being more common in subjects on dialysis than on conservative treatment.

The intensity of uremic pruritus ranges from mild (slightly more than half of subjects), moderate (<40%) and severe and very severe one (about 10%). Pruritus influences patients' psyche and is considered to be the most bothersome symptom by patients with CKD. Itch leads to total restlessness at least in some subjects. There is evidence that uremic pruritus affects patients' sleep quality. Itchy subjects have more problems with falling asleep and, waking up, they report lower sleep quality and worse functional capacity during the day. It was even suggested that uremic pruritus is associated with increased mortality, probably due to the above-described sleep disturbances.

The pathogenesis of uremic pruritus is complex with several factors involved. One may consider hyperparathyroidism, imbalance in divalent ions, accumulation of mast cells with derangement of tryptase and chymase activity, microinflammation and neurogenic abnormalities including distal neuropathy, and disturbed homeostasis of opioid receptors both centrally and peripherally (decreased expression of kappa opioid receptors in the skin). Special attention has focused on the role of xerosis (dry skin) as a factor contributing to the pathogenesis of uremic pruritus or at least its role in aggravating the intensity of itch. Some years ago our group proposed the introduction of an

independent term 'uremic xerosis' to underline its importance in patients with CKD.

It is well known that xerosis is a frequent phenomenon in dialysis patients, affecting about 50-85% of this population. Skin dryness may appear at any stage of CKD, but it is more common in dialysis patients. Skin barrier damage manifesting itself through clinically dry, rough and flaky skin in patients on dialysis may be induced by numerous factors, such as decrease in moisture level in the epidermis and/or sensitivity of horny layer of the epidermis to external damaging factors. One may also point out that atrophy of sebaceous glands, as well as secretory and ductal portions of the eccrine sweat glands, resulting in lower levels of surface lipids of the skin and loss of the integrity of the water content in the stratum corneum, may also contribute to the pathogenesis of uremic xerosis.

The level of glycerol, considered as one of the relevant humectants and a component of natural moisturizing factor, was also documented to be decreased in uremic patients' skin. Recently our group additionally reported disturbed content of epidermal lipids in patients on hemodialysis showing decreased level of cholesterol and triglycerides. Xerosis may be observed in all skin areas, however it seems to be more intense on the lower legs. The corneometry values are usually lower and transepidermal water loss (TEWL) is higher in the skin of uremic patients compared to healthy population. This is true both for adult as well as for pediatric subjects.

The relationship between xerosis and uremic pruritus has been discussed for many years. To the best of my knowledge, Young and coworkers were the first (in 1973) to describe the correlation between pruritus and a level of skin dryness. This was confirmed by other researchers, however some authors were unable to find a direct relationship between xerosis and uremic pruritus. Recently we documented that xerosis occurred significantly more often in patients with uremic pruritus compared to those free from itch. Moreover, skin dryness was more severe in subjects with pruritus. Additionally, the intensity of uremic pruritus was considerably higher in those with dry skin in comparison to patients without clinical symptoms of xerosis. We also documented higher TEWL mean values on the lower legs and on the skin of the abdomen in patients suffering from uremic pruritus. These findings suggest that uremic xerosis has significant influence on uremic itch.

As the pathogenesis of uremic pruritus is not completely clear, there is no single treatment of choice available. Several treatment algorithms have been proposed. However, all the experts agree that reduction of skin dryness and proper care of the skin is the first therapy step in subjects suffering from uremic pruritus. Our experience confirms that restoration of the skin barrier is beneficial in reducing itch intensity. However, it is important to underline that regular application of emollients may be a problem in this group of severely ill patients when continuous treatment is necessary to obtain a long-term effect. Ultraviolet B therapy is regarded as an effective treatment modality, however the availability of the specialized equipment almost exclusively in dermatology units limits its usage.

There are several controlled studies showing effectiveness of gabapentin or pregabalin in uremic pruritus. Nalfurafine, a kappa opioid agonist, is registered only in Japan for the treatment of uremic pruritus. Japanese colleagues report good results using this drug. One may also consider antidepressants, especially serotonin selective reuptake in-

hibitors (sertraline, mirtazapine). These agents, according to the European guideline on chronic pruritus, are regarded as a second- or third-line therapy for different types of chronic itch, including uremic pruritus. Some new agents are under development. One is nalbuphine (a kappa opioid receptor agonist and mu opioid receptor antagonist).

In conclusion, uremic pruritus and uremic xerosis are common phenomena in patients with CKD. They both significantly decrease quality of life and require effective treatment. Close cooperation between nephrologists and dermatologists is essential in providing the best available treatment for these conditions. ■

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Find out more about the journals at the ERA-EDTA booth and the Oxford University Press stand (no. 1.273), where you will also be able to pick up free sample copies of ndt.



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The metabolic risk profile before and after renal transplantation

We need more clinical trial evidence to optimize care and reduce cardiovascular risk

Cardiovascular disease remains the leading cause of death for patients with renal disease, both pre- and post commencement of renal replacement therapy (RRT). National registry data from many countries across Europe and beyond demonstrate the significant cardiovascular mortality risk across the spectrum of renal disease, due to both traditional and renal-specific risk factors. While successful renal transplantation can attenuate mortality risk, even among renal allograft recipients the specter of cardiovascular risk lingers and it remains one of the leading causes of death after renal transplantation. Cardiovascular risk for patients before and after renal transplantation differs from the general population in many aspects. While some of the pathogenesis of cardiovascular disease in renal patients is shared with the general population (since traditional components of the metabolic risk profile are prevalent in renal patients) the influence of non-traditional factors also plays a significant role. This may explain why the weight of traditional metabolic risk factors differs for renal patients, especially those on RRT. Understanding the pathophysiology of cardiovascular death for renal patients is key to attenuating risk, but we must acknowledge the dynamic and conflicting nature of metabolic risk profiles across the spectrum of renal disease.

Chronic kidney disease

Hypertension is both a cause and complication of chronic kidney disease (CKD). Blood pressure control is one of the key strategies to prevent the progression of CKD to end-stage kidney disease (ESKD), with strong evidence for prevention of adverse outcomes with achievement of target blood pressures goals. Tight management of diabetes, the commonest cause of ESKD in many countries, is also associated with positive outcomes. However, difficulty arises with modification of glucose-lowering drugs in the context of deteriorating renal function. Notably, mandatory requirements for the cessation of metformin with estimated GFR < 30 ml/min in many countries is archaic and leads disrupted diabetes management for many patients. With regards to dyslipidemia, the SHARP study demonstrated the benefits of low-density lipoprotein (LDL) cholesterol-lowering therapy in the setting of CKD. Finally, in the case of obesity there is some suggestion from systematic reviews that weight-loss strategies may reduce proteinuria and possibly prevent progressive CKD.

Dialysis

Patients with ESRD undergoing RRT with dialysis are at significantly high risk for cardiovascular events. However, in contrast to CKD, the evidence is limited as to whether tra-

ditional therapies are beneficial. For example, there is no evidence to support a target blood pressure or specific therapy for dialysis patients to prevent adverse outcomes. The control of blood pressure in dialysis patients is also affected by dialysis-specific considerations, such as interdialytic fluid accumulation and greater use of erythropoietin, which further complicate the cause and effect of targeting blood pressure management. In diabetes, while poor glycemic control is associated with development of cardiovascular events and all-cause mortality, we have no evidence for the optimum management of diabetes on dialysis. In addition, monitoring glycemic control for dialysis patients is compromised by sub-optimal glycated hemoglobin measurements in the setting of advanced renal dysfunction. The area where most clinical trial data exist is in dyslipidemia, but this remains predominately negative. Both the 4D and AURORA studies did not identify a significant reduction in events for patients on hemodialysis receiving lipid-lowering therapy. In addition, the SHARP study demonstrated a non-significant reduction in the primary endpoint in the cohort of dialysis patients (both hemodialysis and peritoneal dialysis). Therefore, the evidence supporting lipid-lowering strategies for dialysis patients is not as strong as demonstrated in the setting of CKD. Finally, obesity has been shown to convey an actual survival advantage for dialysis patients. This further confounds our understanding of metabolic risk profiles and introduces the concept of reverse epidemiology for dialysis patients. Understanding these paradoxical findings for dialysis patients is important to enhance our management of metabolic risk profiles in the transition from CKD to RRT. Explanations for the lack of effect include reduced importance of traditional metabolic risks in comparison to the increased prevalence of non-traditional factors on dialysis such as anemia, abnormal bone metabolism and vascular calcification (explaining why many cardiovascular deaths for dialysis patients are non-atherosclerotic in nature). In addition, clearance of drugs on dialysis may attenuate the beneficial effects of pharmacologic therapy and thus limit its impact.

Transplantation

Having considered this metabolically complex environment pretransplant, the situation is further complicated post renal transplantation. Our armamentarium of immunosuppression commonly affects metabolic risk profiles after renal transplantation (Figure 1), and this should be appreciated, especially as cardiovascular disease remains a leading cause of death for renal allograft recipients. The costimulation blocker belatacept looks increasingly promising with regards to attenuation of cardiovascular risk and overall graft survival, according to a recently published article looking at 7-year outcomes in comparison to ciclosporin, and could facilitate tailored immunotherapy. Unfortunately, the paucity of clinical trials intervening on metabolic risk continues in the setting of renal transplantation. The SECRET study, comparing blood pressure control with candesartan versus placebo, was stopped

prematurely as the primary event rate was too low (incidentally, events rates were equivalent in both groups at the time of cessation). Recent evidence from a multicenter clinical trial comparing ramipril to placebo in renal transplant recipients with proteinuria also failed to show any clinical benefit of angiotensin-converting enzyme (ACE) inhibition post renal transplantation. There is plentiful evidence that diabetes (preexisting and also posttransplantation diabetes) is a risk factor for cardiovascular events, but we have no clinical trial evidence to show whether any specific intervention is more beneficial or to show the optimum target or management. The ALERT study specifically explored the benefit of lipid-lowering intervention for renal allograft recipients. While a difference in the composite primary endpoint was not achieved, subanalysis did demonstrate significant reduction in risk for cardiac death or nonfatal myocardial infarct. Obesity at the time of transplantation has shown inconsistent results with regards to its impact upon coronary and / or ischemic events post renal transplantation. However, regardless of body mass index, patient survival is improved by renal transplantation versus remaining on dialysis.

Limitations to our understanding

Our knowledge of metabolic risk pathophysiology across the spectrum of renal disease is limited. For certain risks, such as hypertension and diabetes, there is a U-shaped relationship where polar extremes of both blood pressure and glycemic control are associated with adverse outcomes. We lack understanding on optimized targets for patients with more advanced renal dysfunction and there is a lack of controlled studies on the effect of different therapeutic interventions on cardiovascular events, especially in RRT. Clinical recommendations are based on inference from studies performed in the general population with normal renal function, and we should hesitate to simply translate data from the general to the renal population. The interplay between metabolic and non-metabolic risk factors in cardiovascular pathophysiology among renal patients also requires further investigation.

Conclusion

Metabolic risk profiles before and after renal transplantation are prevalent, dynamic and conflicting in their pathophysiologic implications for adverse outcomes. While renal transplantation alters metabolic risk profiles significantly, predominantly under the influence of immunosuppression, the evidence for treatment remains limited and disparate due to a shortage of targeted clinical trials in this area (Figure 2). Further work is warranted to better understand the prevalence, pathophysiology and optimized management of metabolic risk before and after renal transplantation. We also need to understand the relative importance of metabolic versus renal-specific risks with regards to cardiovascular pathophysiology, especially in the setting of RRT. By doing so, we will be able to offer our patients optimized care to attenuate their significant cardiovascular risk. ■

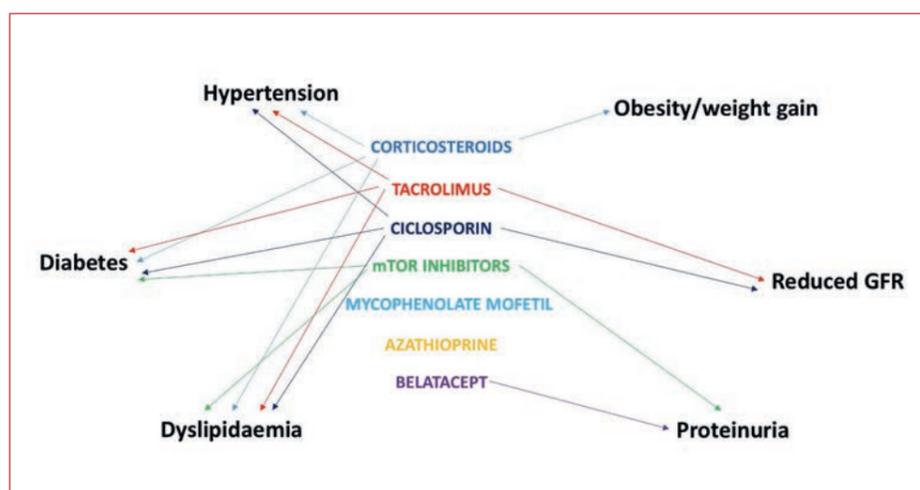
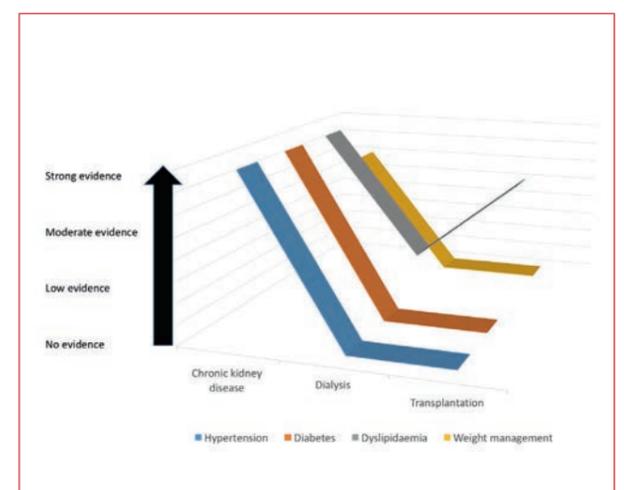


Figure 1: Impact of immunosuppression on metabolic risk profile
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Figure 2: Strength of evidence for management of metabolic risk profiles across renal spectrum
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GEORGE S. REUSZ
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Extracorporeal treatment of immune mediated kidney disease

Introduction

Immune-mediated kidney disease (IMKD) is one of the greatest challenges in nephrology. Due to the complexity of the underlying pathomechanisms, our therapeutic armamentarium is often polypragmatic and still insufficient. SLE nephritis, anti-basement membrane disease, ANCA vasculitis, aHUS due to antibodies against complement factors, TTP due to antibodies against ADAMTS13 and antibody-mediated kidney rejection are illustrative examples of IMKD involving antibodies and immune complexes. Immune mechanisms play a role in the mechanism of non-inherited FSGS, however the circulating factor has not yet been identified. Extracorporeal treatment (ECT) is applied to eliminate pathologic substances from the plasma, based on the assumption that their removal will reduce further damage and may reverse the pathologic process. The pathologic substance may be an autoantibody, immune complex, myeloma light chains, cryoglobulin, cholesterol-containing lipoprotein, or other substance. ECT thus appears to provide a logical option in the treatment of IMKD. There are a number of theoretical and practical considerations that may help us to find the role of ECT in the chain of therapeutic modalities involved. Theory also has to be supported by practical experience, so there is a need to summarise our knowledge in consensus documents and guidelines in order to avoid over-zealous use of potentially harmful procedures.

The forms of ECT (Figure 1). Most common ECT options.

Classic therapeutic plasma exchange (plasmapheresis) separates and removes the pathogen by centrifugation or filtration. While the centrifugation method needs specifically designed machines, the membrane separation method is based on existing dialysis machines. Centrifugation is accordingly the method preferred by haematology or blood bank-based physicians, whereas membrane filtration is preferred by nephrology-based physicians. A recent survey among leading European paediatric nephrology units revealed that membrane filtration was the most common technique, with albumin being the most frequently used substitution fluid and heparin the preferred anticoagulant.

Further processing of the patient's plasma: innovative ECT techniques.

Double filtration, cascade filtration, immunoad-

sorption. These procedures can be divided into three stages: (1) the patient's plasma is separated from the cellular components of blood using centrifugation or filtration, (2) the isolated plasma once again undergoes separation through additional filters using hollow fibre technology or specifically designed high-affinity columns and (3) the 'cleansed' plasma is then returned to the patient. Double filtration: the second filtration procedure through a membrane with pores of smaller diameter allows the removal of particles bigger than albumin, such as immunoglobulins and immune complexes. It causes simultaneous removal of particles larger than the antibodies, such as fibrinogen, α -2 macroglobulin or IgM immunoglobulins, which may influence the rheological properties of blood. As the patient's own purified plasma is reutilised there is no need for donor plasma or albumin during this procedure. Immunoabsorption (IA) is performed with high-affinity columns selectively binding human immunoglobulin and IC while neither removing other plasma proteins nor necessitating substitution with albumin, fresh frozen plasma or immunoglobulins. Available immunoabsorbents contain staphylococcal A protein (Prosorba, Immunosorba) or immobilised sheep antigens (Therasorb) or Gam 146, a synthetic peptide with binding properties (GAM-columns, Globaffin) similar to those of A protein. Biospecific synthetic columns have also been created to remove the ABO blood group-specific antibodies (Glycosorb-ABO) from a potential solid organ recipient.

Most common side effects of ECT. We have to keep in mind that all types of ECT involve considerable risk to the patient. The overall mortality of TPE is 0.03 to 0.05 percent; death is most commonly due to respiratory or cardiac complications. ECT should be executed according to specific rules and under strict quality control. Eliminating immunoglobulins from the patient's plasma is a non-selective procedure, so it increases the risk of infection per se. Anticoagulation either by citrate or by heparin has to be strictly controlled, as bleeding or thrombosis, citrate toxicity or heparin toxicity (heparin-induced thrombocytopenia) may ensue. Bleeding may also be the consequence of coagulation factors being eliminated. The prevalence of complications in relation to central lines (infection, thrombosis, venous occlusion and embolism) may be as high as 20%. Allergic reactions to blood products are common (mainly FFP (10-20%), rarely to albumin (1-5%)). Infection by blood-borne agents is rare, but in the case of FFP it is still present. Further complications to keep in mind are transfusion-related acute lung injury (TRALI), and ACI inhibition-related reaction.

The place of ECT in the treatment of IMKD. As IgG has a half-life of about 21 days, the plasma concentration would

only fall by 50 percent after three weeks, even if immunosuppressive therapy could immediately halt new antibody production. Such a delay is unacceptable with an aggressive autoantibody, as seen in ANCA positive vasculitis or anti-GBM antibody disease. The complementary elimination of pathogenic autoantibodies by a highly efficacious ECT technique is therefore a real therapeutic option. Another potential benefit of ECT is its capability to unload the reticuloendothelial system (thereby enhancing endogenous removal of circulating antibodies and immune complexes) and the possibility of (re-)infusing large volumes of plasma without the danger of intravascular volume overload. Elimination of autoantibodies is a double edged sword, however, as it may stimulate pathogenic clones and once ECT has stopped the antibody levels may raise rapidly to reach or even exceed the initial levels. On the other hand, we may take advantage of this stimulation to enhance the efficacy of our cytotoxic / immunosuppressant therapy. Steroids, cyclophosphamide and / or rituximab are commonly used as immunosuppressants concomitantly with ECT. As rituximab is eliminated by plasma exchange, it is usually administered at the end of the ECT procedure.

Evidence-based indications. Theoretical considerations based on pathophysiological principles should always be proved by clinical evidence. The difficulty is that it is not possible to perform randomised controlled studies; seriously sick patients are often pre-treated with immunosuppressants while ECT is used as an ultima ratio. Thus, much of our knowledge and experience is based on case reports and small series of patients with corresponding levels of evidence. Nevertheless, various societies and organisations (ASFA: American Society for Apheresis, BCSH: British Committee for Standards in Haematology) have published extensive, rigorously graded categories concerning the indications of ECT. The ASFA guidelines are collected in an alphabetical list of indications with broad treatment recommendations. However, some aspects of the clinical management of patients / donors undergoing apheresis and of the service as a whole are not considered in detail. To cover these practical issues, the British Committee for Standards in Haematology (BCSH) published its revised guidelines in 2015. These two guidelines are actually the basis of how to indicate, plan and perform ECT. The growing list of possible indications now includes new entities beyond classical IMKD, primarily from transplantation medicine: antibody-mediated rejection after solid organ transplantation or preparation for transplantation from an ABO-incompatible donor.

Examples. Our tertiary centre for paediatric nephrology performs therapeutic plasma exchange using the filtration technique, similarly to the majority of European paediatric nephrology units. Our experience with TMA cases caused by antibodies to complement factor H (aHUS, four cases) and by antibodies against ADAMTS13 (TTP, two cases) is an excellent example of the role of ECT and concurrent sequential immunosuppression. All our aHUS patients were diagnosed before the eculizumab era and treated with plasma infusions, plasma exchange and achieved a first remission of TMA. All were also treated with concomitant immunosuppression (IS) comprising steroids, cyclophosphamide, and with rituximab after stopping ECT. With this approach to treatment, all four patients with FH antibodies and the TTP patients with ADAMTS13 antibodies came into sustained remission. All six patients have now been in immunosuppression-free remission for more than 22 months (range 20.3-62.8). Indeed, additional studies are needed to establish the respective place of eculizumab, PE, cyclophosphamide pulses, rituximab and MMF for optimal treatment of antibody-associated TMAs.

Conclusion and new horizons. In many indications, elimination of pathologic substances in IMKD is a first- or sec-

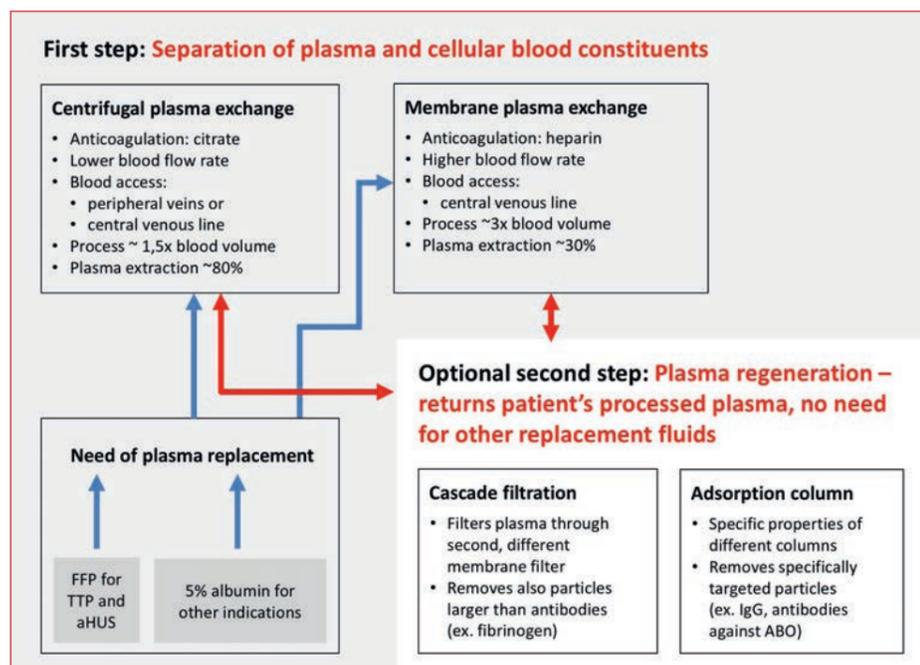


Figure 1: The forms of ECT
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ond-line treatment option, usually combined with concomitant/sequential immunosuppressive therapy. As our experience grows, the spectrum of diseases is in constant evolution, so we need a regular update of our knowledge regarding indications and new technical options. Technological development and the introduction of new columns with specific and differentiated absorbing capacities (immunoglobulins, blood group antigens etc.) has opened a new horizon, but economic and financial considerations may hamper their introduction into everyday practice. With these new techniques, ECT may be used not only in therapy, but also in preparation for interventions such as transplantation through the ABO blood group barrier, or the elimination of preformed donor-specific antibodies. ■

References

1. Schwartz J et al. Journal of Clinical Apheresis 2013, 28:145–284
2. Howell C et al. Transfusion Medicine, 2015, 25, 57–78

Sclerostin and the CV System



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Canonical Wnt signalling activity contributes to physiological and adaptive bone mineralisation and is an essential player in bone remodelling. Sclerostin is a prototypic soluble canonical Wnt signalling pathway inhibitor, which is produced in osteocytes and blocks osteoblast differentiation and function. Therefore, sclerostin is a potent bone inhibitor of formation and mineralisation. Accordingly, rodent sclerostin deficiency models exhibit a strong bone phenotype. Moreover, blocking sclerostin via monoclonal antibodies represents a promising treatment perspective against (postmenopausal) osteoporosis. Together with FGF23, sclerostin is the second osteocytic product which turns the osteocyte to be a secretory and endocrine cell of outstanding importance in bone and mineral metabolism. The osteocyte is indeed part of a regulatory system with significant impact upon at least mineral metabolism, bone metabolism and also cardiovascular function. Beyond the bone field novel data definitely show that Wnt signalling in general and sclerostin in particular are associated with ectopic extraosseous mineralisation processes, as evident in cardiovascular calcification or calciphylaxis. The latter is a devastating calcification condition with high morbidity and mortality. Uremia is characterized by the parallel occurrence of disordered bone mineralisation and accelerated cardiovascular calcification (chronic kidney disease – bone and mineral disorder, CKD-MBD), linking skeletal and cardiovascular disease – the so-called bone-vascular calcifi-

cation paradox. In consequence, sclerostin may qualify as an emerging player in CKD-MBD and sclerostin may actually be a very important player in this bone-vascular paradox. Recent years have produced increasing evidence regarding the rapidly evolving field of how sclerostin participates in CKD-MBD. Starting from data originating in the classical bone field current sclerostin research is focussing at the three major areas of CKD-MBD and how sclerostin is participating in these areas, i.e. disturbed mineral metabolism, renal osteodystrophy, and uremic cardiovascular disease. Recent research findings underline the need to revise the potential importance of sclerostin in CKD, by focusing on how sclerostin research is gradually evolving from the classical osteoporosis niche into the area of CKD-MBD. Several important open questions remain which should guide future research towards:

- Assay reliability and comparability for sclerostin measurements in serum particularly in CKD / ESRD patients.
- It needs to be elaborated whether and to what extent nephrological standard of care alters levels of sclerostin and what that means in turns of patient outcome.
- It appears crucial to finally clarify to what extent circulating sclerostin levels in CKD patients originate from the vasculature or the bone.
- Further research is needed to explore to what extent increased local and or systemic sclerostin activities contribute to renal osteodystrophy in general and particularly to adynamic bone disease.
- The potential contribution of Wnt signalling in uremic vascular disease as reflected e.g. by local tissue activities of sclerostin fuels speculations about a contribution of Wnt signalling in accelerated uremic arteriosclerosis. More research is needed to clarify the role of sclerostin as pro- or anti-calcific.
- Finally, the safety and efficacy of blocking sclerostin in human CKD-MBD should be carefully evaluated because this approach may carry some risks but at the same time also fascinating perspectives in CKD-MBD patient care. ■

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**FRANCESCO
LOCATELLI**
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Is online HDF the new standard for extracorporeal therapy?

The aim of hemodialysis (HD) is to control fluid overload, correct electrolyte imbalance and metabolic acidosis, and remove solutes that are normally excreted by the kidneys. Unfortunately, standard low-flux HD is not very efficacious compared to healthy kidneys, and patient morbidity and mortality rates are still very high.

High-flux hemodialysis (hf-HD) is an alternative and efficient dialysis technique which was introduced many years ago, based on the hypothesis that the high morbidity and mortality rates of low-flux HD were partly due to inadequate removal of middle molecule solutes.

High-flux membranes remove solutes of higher molecular weight, such as β 2-microglobulin (11.8 kDa) and show high biocompatibility, thus reducing the activation of several cellular mechanisms and biological systems that cause chronic inflammation and oxidative stress.

On-line HDF is considered the most efficient technique for using high-flux membranes, as clearances of small solutes such as urea are higher than in hemofiltration (HF), and clearances of middle molecule solutes, such as β 2-microglobulin, are higher than in hf-HD.

Cardiovascular instability is the most frequent clinical problem in dialysis patients. The importance of preventing intradialytic hypotension is mainly related to the reduction of organ ischemia and the need to achieve the patient's dry body weight, so controlling hypertension better than in hemodialysis patients is mainly dependent on fluid overload.

A better hemodynamic stability of online HDF was reported by Locatelli et al. in an Italian randomized study. Reduced sodium removal was considered to be at least partly responsible for better cardiovascular stability.

An alternative hypothesis by Maggiore et al. suggested blood cooling as the main blood pressure stabilizing factor in on-line HDF.

Some studies have examined the association between delivered convection volume and mortality outcomes. The prospective cohort Dialysis Outcome Practice Patterns Study (DOPPS) reported that the mortality risk was 35% lower in European patients receiving a minimum of 15 L/session of replacement fluid (~17 L of convection volume) than in the control population receiving standard HD, even after adjustment for many variables, including age, comorbidities, urea clearance and local practice patterns.

An Italian prospective observational study of >700 patients over a 3-year period also reported that high-volume HDF was associated with lower mortality risk.

An important criticism is that this dose and effect relationship is in fact due to a selection bias, with high convection volumes only being achievable in the more healthy patients, and thus with a low mortality risk. It is true that while extensive statistical adjustments did not alter the results, residual confounding still remains.

ESHOL is the first randomized study showing a significant advantage for OL-HDF in all-cause mortality, stroke mortal-

ity and infection-related mortality. Interestingly, this trial had the highest achieved convection volumes (22.9–23.9 L/HD session). Unfortunately, these positive results were not confirmed by the other two largest randomized trials (CONTRAST and TURKISH studies).

However, it is intriguing that post hoc analyses of the three largest randomized studies on survival in online HDF (CONTRAST, TURKISH and ESHOL) showed that patients who received the highest convection volumes were associated with a lower mortality and cardiovascular events than those randomized to HD, thus supporting the findings of the international observational DOPPS study, published many years ago and referred to above.

Unfortunately, the majority of the patients in these trials did not reach the target exchange volume. It is very likely that the exchange volume was related to vascular access flow, and probably related to better vessels, thus possibly affecting patient survival as well. Moreover, in ESHOL, post hoc exclusion occurred if the pre-set 18L were not reached. A selection bias could thus be a possible explanation for the results of the post hoc analyses of these trials, since the possibility that larger reinfusion volumes could be facilitated in patients with better vascular access and intradialytic cardiovascular stability cannot be ruled out.

Three meta-analyses have recently been published in an attempt to clarify these aspects. The meta-analysis by Wang et al. included 16 studies, 2 of which were crossover (3,220 patients in total). According to the authors, no significant difference was found in the overall risk of mortality and cardiovascular events between patients treated with HF and HDF and HD, despite a relative numerical risk reduction of 15% and 17%, respectively. It is noteworthy that a significant 51% reduction in intradialytic symptomatic hypotension was found in patients treated with the convective techniques, which are associated with a significant reduction in 2 microglobulin predialytic mean plasma levels of 5.96 mg/L, without a significant difference of the clearances of small molecules evaluated as KT/V of urea.

In their meta-analysis, Nistor et al. included 35 randomized trials, of which 17 were crossover (4,039 patients overall). No significant advantages of convective techniques were shown in comparison to the prevalent diffusive techniques, although a numerical reduction of 13% was seen. It is noteworthy that a significant 25% reduction in cardiovascular mortality and a significant 28% reduction in intradialytic symptomatic hypotension were found in patients treated with convective techniques. No significant benefits were observed with regard to non-fatal cardiovascular events and hospital admission.

Susantiphong et al. included 65 studies in their meta-analysis, 29 of which had a crossover design (12,182 patients overall). They found a significant mortality reduction of 16% and a 45% reduction in intradialytic symptomatic hypotension in patients treated with convective techniques in comparison with the patients treated with prevalent diffusive ones.

The three reported meta-analyses on the topic have underlined the methodological limitations of the trials included, so their conclusions should be carefully evaluated. However, all three meta-analyses showed a significant reduction in intradialytic symptomatic hypotension in patients treated with convective techniques in comparison with the patients treated with prevalent diffusive ones, although the interpretation of these findings is still a matter of discussion.

Peter et al., on behalf of the HDF Pooling Project investigators, conducted a pooled individual participant data analysis of randomized controlled trials in order to provide more reli-

able evidence for the effects of HDF on mortality outcomes. After a median follow-up of 2.5 years, 769 of the 2793 participants had died (292 cardiovascular deaths).

Online HDF reduced the risk of all-cause mortality by 14% and of cardiovascular mortality by 23%.

There was no evidence of differentiated effects in subgroups. The largest survival benefit was for patients receiving the highest delivered convection volume (>23 L per 1.73 m² body surface area per session), with a multivariable-adjusted HR of 0.78 for all-cause mortality and 0.69 for cardiovascular disease mortality.

In conclusion, no conclusive data are available at present concerning the effect of online HDF on survival and morbidity in hemodialysis patients.

Convective treatments are also able to facilitate the removal of sodium and water overload, thus allowing better intradialytic vascular stability. It is possible that the positive effects of convective treatments are mainly related to better fluid control, less intradialytic hypotension and thus less intradialytic organ ischemia, including myocardial stunning.

It is important to underline that it is very difficult to demonstrate the positive effects of convective treatments in randomized controlled trials, where there is a selection bias of motivated participating centers, including doctors, nurses, and patients, thus possibly improving the outcomes of the patient in the control groups also. Purely randomized control trials targeting different convection volumes are required to determine a dose-response effect definitively. Positive outcomes of online HDF are even more difficult to confirm in everyday clinical practice, given the much lower expertise and the motivations of the teams, and the lower risk of selection bias among patients.

A new DOPPS analysis involving a much larger patient population is on the way, and the results are being anticipated with great interest, in order to further clarify the effect of online HDF on survival and morbidity of hemodialysis patients, and whether high convection volumes are actually a crucial aspect for achieving better outcomes with HDF in comparison to standard hemodialysis, including high flux dialysis, in everyday clinical practice. ■

References

1. Francesco Locatelli Leano Violo Selena Longhi Lucia Del Vecchio Current Evidence in Haemodiafiltration *Blood Purif* 2015;40(suppl 1):24–29



Leading European Nephrology

54TH ERA-EDTA CONGRESS



Cristina Ortiz, "Moving forward", 2014,
mixed technique, 120 cm x 70 cm, from the exhibition "Aspirations"



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Next Year – Madrid!

Expert in Interview

► **PROF. JORGE B. CANNATA-ANDIA**
54th ERA-EDTA Congress President



From 3–6 June 2017, Madrid will be the venue for the 54th ERA-EDTA Congress. This great event will occur 18 years after the last time we met in Madrid, which was also the

last ERA-EDTA Congress of the 20th century (1999)! Since then, ERA-EDTA Congresses have experienced tremendous growth, with the number of participants tripling. Over this time, the ERA-EDTA itself has also progressively expanded, leading European nephrology into the 21st century by developing several major initiatives such as the modernization of the Registry, continuing the development of the two journals of the Association (NDT and CKJ), promotion of active collaboration with many European and other medical societies, creation of the ERA-EDTA Working Groups and supporting more than 30 European CME courses every year. Many of these fruitful activities will contribute to the scientific content of the 54th ERA-EDTA Congress in Madrid. In addition, the plenary lectures will cover topics considered to be at the forefront of biomedical knowledge, such as new approaches to kidney regeneration, neural modulation of the immune system, and lipotoxicity and metabolic syndrome. During the Congress, ERA-EDTA will offer more than 60 symposia, 30 mini-lectures and many CME Courses. The whole spectrum of clinical and translational nephrology, dialysis and transplantation will be covered, as well as the discussion of specific topics such as the relevance of studying large CKD cohorts, the importance of CKD as a clinical and experimental model of premature aging, renal imaging, renal histopathology, and CKD guidelines, among others. All these exciting themes will be covered by

expert speakers from more than 30 countries. I am sure that Madrid will once again be a friendly place to discuss science and to meet old and new friends alike. ■

We hope you will join us at the ERA-EDTA Congress in Madrid 2017!

**Professor Jorge B. Cannata-Andía,
54th ERA-EDTA Congress President**



The SCOPE project aims to assess existing methodologies for CKD screening among older adults using real-life data from a cohort of 75+ patients and to investigate potentially useful application of existing and innovative biomarkers of CKD in older people. Furthermore cost-effectiveness of existing and innovative CKD screening strategies in a population at high risk of developing end stage renal disease (ESRD) will be evaluated.

The SCOPE study will be an observational multinational, multicenter, prospective cohort study targeting CKD screening in community-dwelling subjects aged 75 years or more, consecutively referring to outpatient clinics at participating institutions. The primary endpoints will be the rate of eGFR decline and the incidence of ESRD (being defined as GFR <15 mL/min/1.73 m²). Among the secondary endpoints are kidney function decline as estimated by novel application of existing biomarkers, changes in biological and molecular markers linked to aging process, CKD complications (such as anemia, hyperphosphatemia, acidosis etc.), incidence of major comorbidities, overall and cardiovascular mortality, adverse drug reactions, self-reported disability and objectively measured physical performance decline, cognitive impairment, depression, malnutrition, health related quality of life and health resource consumption.

The Scope project will therefore build a strong European database of patients with chronic disease older than 75 years and evaluate the impact of CKD on morbidity, mortality and quality of life for this cohort of people. Built on this strong evidence the SCOPE Consortium will formulate "European Recommendations and Guidelines" and will establish a "European Educational Program" for EUR citizens as well as EU health care professionals. ■

Imprint



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What's on in Vienna today?



Chagall to Malewitsch

The Russian Avant-Gardes
Albertina
Daily, 10.00 – 18.00



Special exhibition: "So this is the strong Sex." Women in Psychoanalysis

Sigmund Freud Museum
Daily, 10.00 – 18.00



Wiener Staatsoper live outdoors

Selected opera and ballet performances from the opera house on Ringstrasse are broadcast live on a 50 m² LED video screen outside the opera house.

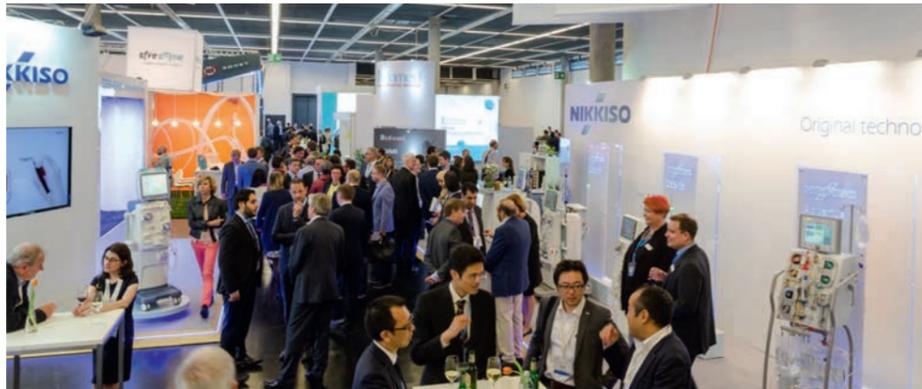
Monday, 23 May, 19.30
LA TRAVIATA, Giuseppe Verdi



Jazz at Monday's Finest

The Austrian jazz scene presents itself every Monday from 7.00 pm to 9.00 pm at free after-work concerts in the Wein & Co Bar on Naschmarkt. The slogan is: Soulful Wine – Sunset Jazz. Today, Richard Oesterreicher Quartet "Toots Thielemans meets Brazil"

53rd Congress Vienna Austria May 21st-24th 2016



Impressions from Day 1 & 2

