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## Nephrology has to become more progressive – like the artists in Vienna at the turn of the 20<sup>th</sup> century

*Interview with the ERA-EDTA Congress President, Professor Gert Mayer*

**Professor Mayer, the main theme of the Congress is "From big data to personalized therapy – bio-statistics meets molecular medicine" – how does the program of the Congress reflect that?**

**MAYER:** The conference theme is found in the plenary lectures, first of all. The first plenary lecture by Andrew Kasarskis demonstrates how large volumes of data can be used to characterize patients better and in that way to pave the way for personalized medicine. The 'big data approach' says that in order to try to read a system everything can be analyzed without having formed a hypothesis before. This approach and the form of purely hypothesis-driven science practiced until now are still seen as complementary – rather than being polar opposites, I think they go hand-in-hand. In other words, information technology and analysis techniques give us totally new opportunities, but these do not stand in competition with the conventional scientific approach, as the first presentation will show. The second presentation, by Nicholas J. Schork, with the provocative title 'Is it time for one-person trials?', describes how, once patients are characterized much more precisely using the 'big data approach', clinical research has to change – especially in the way that studies are conducted. Nicholas J. Schork has a background in oncology – and the oncologists are already further advanced in using and processing more patient data than we nephrologists. They classify tumors nowadays completely differently than even just a few years ago, and are striking out successfully in new directions toward personalized therapy. The third plenary lecture, 'Transplantation tolerance: can it turn into a reality?', given by Kathryn Wood, then describes the field within nephrology where the 'big data approach' could first be applied: namely the field of transplantation immunology. Patients are still being characterized using just a few parameters. But there is room for more, and if immunological characterization of patients and transplant selection could be done even more precisely, this could result in fewer rejections and losses of transplants. Actually, I am very curious to hear Kathryn Wood's views on the matter!

**What are the other main highlights of the scientific program, in your opinion?**

**MAYER:** The program has many highlights, and the 'Late Breaking Clinical Trials' session is certainly one of them. The ERA-EDTA Registry session is another highlight, for sure.



**GERT MAYER**  
Innsbruck, Austria  
President of the  
53rd ERA-EDTA Congress

The joint session with 'The Lancet' has major importance – our partnership with this highly renowned journal will further sharpen ERA-EDTA's profile as one of the leading scientific societies worldwide. Since you are also asking about my personal favorites, let me say that I am personally very interested in 'The gut and renal axis' session. The interrelationships between the gastrointestinal tract and kidney function are a new field of research and extend far beyond the phosphate metabolism – some exciting issues, such as the role of the gut microbiome in uremic toxin formation, or whether uremic symptoms can be mitigated by altering the composition of the microbiome, are currently being discussed. The session on 'Frail and elderly patients with CKD' has enormous clinical relevance, as they form the main group of patients in our care, of course, and because there are numerous other aspects to be taken into consideration besides the nephrological – geriatric issues, the nutritional dimension, the treatment of many concomitant diseases, as well as social and indeed ethical issues such as discontinuation of dialysis. The average age of dialysis patients has increased over the last decade, and we have to address the challenges that this entails.

**I see – the Congress program really covers the whole spectrum of nephrology. But to what extent does the program bridge the usually wide gap between basic research and clinical nephrology?**

**MAYER:** Many of the sessions attempt to combine basic research and clinical practice. That has not always been possible, of course, but our basic approach has been to avoid

## Expert in Interview

▶ **PROF. GERT MAYER**  
President of the 53rd ERA-EDTA Congress



sessions dealing with either basic research or clinical nephrology, but rather to combine the two and thus inject life into the bench-to-bedside concept. Let me give you an example – Hypoxia in Kidney Disease. The identification by basic research of different hypoxia signals has led to the development of therapeutic interventions that have even found their way into the clinic. In the session on hypoxia, both basic researchers and clinical practitioners will report on their work. This networking, and the reciprocal feedback this allows, is of key importance for further innovations, in my view, and our congress is intended to be a forum for this kind of exchange.

#### What do you think makes this Congress especially attractive for young nephrologists?

MAYER: What I have just been describing is one reason, I believe – the design of sessions, in which a topic is covered from scratch, right up to clinical applications. That can be very attractive for young people, in particular. They get a complete overview and can understand the complex interrelationships that are involved, even when the particular theme does not have a bearing on their own field of specialization. Another advantage is that the ERA-EDTA congress covers the entire range of nephrological themes. Newcomers to nephrology but also more advanced colleagues can experience the discipline in its totality. The congress provides further education that is broad-based

and at the same time at an extremely high level. Then of course there are activities like those of the 'Young Nephrologists Platform' (YNP), which organizes its own symposia. These are particularly interesting for young researchers, naturally, and can also serve as a kind of 'anchorage' for young participants at the congress. The YNP is very active, in general, and an interesting forum for young scientists and clinicians.

#### You chose the Congress logo, in which we see a golden cupola. What exactly is displayed?

MAYER: The picture shows the golden dome of the Vienna Secession building, which the Viennese unflatteringly call the 'Krauthappel' (cabbage). The Secession was a movement of radical artists, Gustav Klimt being the best known, who broke away from the rigidities of the established Austrian art scene and tried to create new styles of art. They erected this Secession building for their own exhibitions, as a kind of congress center, so to speak. I chose this motif as an icon for the Congress not just for its architectural beauty – Vienna has plenty of that – but also for its symbolic character. The Secessionists went beyond the narrow boundaries of convention and were inspired by other fields and disciplines. I think this is the point where nephrology finds itself today: We want to leave the beaten track and explore avenues beyond the conventional, which also means integrating new ways of seeing and new techniques into

our discipline. Nephrology has to become more progressive – like the artists in Vienna at the turn of the 20th century!

#### Speaking of Vienna – what should participants from abroad who are in Vienna for the first time make sure they see or do?

MAYER: There are many excellent theaters, opera houses and museums to suit every taste, many galleries for modern art, and the Secession always has fantastic exhibitions as well. To get a feeling for Viennese flair, however, you can just stroll along the Ringstrasse, a magnificent, artistically designed and landscaped boulevard that has been meticulously preserved. Visitors should also go to one of the traditional wine taverns, called 'Heurigen' – that's a 'must-do'.

#### What culinary specialties should they try? Austria is famous for its cuisine...

MAYER: There are so many Austrian specialties – the cuisine is very eclectic: Tafelspitz (boiled fillet of beef), Wiener Schnitzel (Viennese cutlet), or those with a sweet tooth can try Apfelstrudel and Kaiserschmarrn. So there's a lot going on in Vienna, not just in culinary, but especially in nephrological terms! It is my great pleasure and honor to welcome all of you to the congress. I am sure, its scientific sessions and symposia are as attractive as Europe's most charming city. I wish all those taking part a wealth of interesting contributions and discussions! ■

## ERA-EDTA MEMBERSHIP INFO

### ERA-EDTA Council Members Elections

ERA-EDTA Full Members! Don't forget to vote for the future ERA-EDTA Council candidates!



**Peter Blankestijn**  
The Netherlands



**Annette Bruchfeld**  
Sweden



**Giovambattista Capasso**  
Italy



**Bruce Hendry**  
United Kingdom



**Rainer Oberbauer**  
Austria



**László Rosivall**  
Hungary



**Itzhak Slotki**  
Israel



**Goce Spasovski F. Y. R.**  
Macedonia

All full members of the ERA-EDTA will be able to vote for a maximum two (2) candidates.

The voting station, located next to the ERA-EDTA Membership Office, in the Registration Area, will be open from 21–22 May 2016 during the opening hours of the Registration Desks. On 23 May 2016 the voting station will close at 09.00. Voting will also be possible immediately before the start of the General Assembly, which will take place from 09.30–10.45 on Monday 23 May 2016 in Hall G, Level-2, Austria Center Vienna.

If a full member has lost his / her voting credentials, a valid identification document (i.e. a passport or national identity card) will be required in order to receive them again. Voting by proxy is NOT possible. A short curriculum for each candidate will be on display at the voting station as well as on the ERA-EDTA website.



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#### ERA-EDTA Membership Desk info

**Are you a nephrologist? Do you want to be part of the most authoritative European Association in this field? Become a member of ERA-EDTA today!**

All the information at the ERA-EDTA booth in the Exhibition area or ERA-EDTA Membership Desk in the Registration Area of the Austria Center Vienna.

The ERA-EDTA Membership Desk is located in the registration area of the Austria Center and will follow the same schedule of the Registration Desks.

# Our preventive and early detection activities could be emulated throughout Europe

Interview with Professor Karl Lhotta, President of the Austrian Society of Nephrology



**KARL LHOTTA**  
Feldkirch, Austria  
President ASN

## Professor Lhotta, this Congress is a joint meeting of the ERA-EDTA and the ÖGN (Österreichische Gesellschaft für Nephrologie). To what extent does the scientific program reflect Austrian topics and speakers?

**LHOTTA:** I think the Austrian influence on the congress program is clearly discernible. There are many Austrian nephrologists who are actively involved in the program, and special mention can be made of the 'Lipids in Nephrology' session, in which no fewer than three Austrian colleagues are participating – which is not surprising considering that lipid therapy for CKD patients is a topic that nephrology researchers at Austrian universities have focused on for years. Our General Meeting will also be held during the congress and will include a presentation of the Austrian Dialysis and Transplantation Register, as well as the conferral of our research awards and the ERA-EDTA grant.

## What are the advantages of organizing a joint meeting together with the ERA-EDTA – and what is your experience of collaborating with the ERA-EDTA?

**LHOTTA:** Collaboration has been perfect and for us, as a rather small society in terms of membership, it has been an exciting experience to work with a major international organization in which many processes are professionalized. The Austrian Congress for Nephrology is otherwise held jointly with the Austrian hypertensiologists, and is attended by around 300 people. So a congress attracting more than 7,000 participants from all over the world is on a completely different scale, of course, and we are delighted to be part of it!

## Are there any sessions or talks that you see as THE highlight of the Congress that no-one attending should miss?

**LHOTTA:** It's important not to miss the welcome ceremony, I think – especially the lecture that Professor Raymond Vanholder will be holding then, and in which he will accentuate the importance of chronic kidney disease prevention for the healthcare economy in general. Here in Austria, CKD prevention is currently a key topic that has also become a public issue, so for that reason I am also interested in the European perspective, of course. But there are numerous other highlights – the program is very broad-ranging and has something to offer for everyone. Personally, I am looking forward to the NDT Polar Views on the question 'Should we correct vitamin D deficiency/insufficiency in CKD patients with inactive forms of vitamin D or just treat them with active vitamin D forms?', which is a fascinating topic. Controversial discussions are always examples of real scientific endeavor. Of course, there are many other symposia that are also highly interesting for me, for example the sessions entitled 'Kidney in systemic inflammatory diseases' and 'Membranous nephropathy: new insights', but listing all of them would be going too far.

## Which general challenges does nephrology face in Austria?

**LHOTTA:** One challenge we face in Austria is that we still don't provide full coverage with referral centers for nephrology. However, we believe that such coverage is urgently needed in order to care for patients with complex kidney diseases, and we are now pushing for that. The other major challenge is attracting young physicians and researchers to specialize in nephrology. We are facing the same problem in that respect as European nephrology in general – we have to make young physicians more aware of nephrology and instill greater enthusiasm for this particular discipline. I hope that the ERA-EDTA Congress in Vienna will contribute towards that. Perhaps a few young colleagues or medical students will find their way there and discover that this is an exciting field that is worth getting into! At a more fundamental level, of course, the high and increasing prevalence of dialysis patients is a problem that has to be tackled. Prevalence is continuing to rise, even though we have relatively good transplantation rates in Austria. We have the opt-out solution, and our donor recruitment is also very well organized. At present, we have 24 donors per million inhabitants and our declared aim is to increase that figure to 30 per million. There is currently a discussion in Austria about whether donation after cardiac death should be accepted and pursued, as is already the case in the Netherlands or in the UK, for example. That would definitely produce a significant increase in the number of available organs. Our patients currently wait an average of 42 months on a donor kidney. That figure should certainly be improved, although it is already very good compared to various neighboring countries.

## Cornerstones of the 60/20 prevention strategy in Austria

Education and prevention are paramount aims of kidney care. To that end, the Austrian Society for Nephrology has developed the '60/20' concept. It defines when a CKD patient should be seen by a nephrologist:

- Assignment of patients to a nephrologist or to a central unit by the general practitioner when kidney function is reduced (to 60 % kidney function) and a risk constellation exists.
- Assignment of patients to a nephrologist or to a central unit when kidney function is reduced to 20 %, for comprehensive information about the available options and for decision-making on the optimal form of renal replacement therapy.
- Establishing a sufficient number of central units so that patients can be optimally assigned both medically and organisationally.
- Additional measures (transplantation coordinators, etc.) in hospitals to improve the number of post-mortem donors and to improve collaboration between the disciplines involved.

## Is there anything European nephrology can learn from Austrian nephrology?

**LHOTTA:** Perhaps the excellent way we organize transplantation, with many local transplantation officers who are very dedicated and committed to providing support. Special mention also needs to be made of our dialysis and transplantation registry, which include every single patient up to now, from the first patients who received renal replacement therapy in the 1960s. Although voluntary, all Austrian dialysis units participate and submit their data. The registry includes the diagnosis, comorbidities, laboratory and treatment data of all patients on renal replacement therapy. So it provides us with an excellent epidemiological overview. That's important, because even in a country as small as Austria there are relatively big differences in incidence and prevalence between the regions. Our preventive and early CKD detection activities could also be emulated throughout Europe. Initiation of the 60/20 project deserves special mention (see infobox), which is currently running in two of the nine federal states in Austria, and soon in three. Policymakers in Austria have committed themselves to improving early detection and care, and that is a boost for the project. Our collaboration with general practitioners is also exemplary. Four times a year, we publish a nephrological supplement for the family doctors' journal, which sensitizes those colleagues to nephrological issues. In that way, we manage to focus greater public attention on CKD prevention.

## I asked Prof. Mayer what participants from abroad who are in Vienna for the first time should make sure they see or do. What is your insider's tip – and is there anything you would advise against?

**LHOTTA:** Well, I assume that many people attending the congress will flock to the Upper Belvedere and will want to see the Klimt exhibition. Very beautiful, to be sure, but also very crowded. My tip for those who would like to enjoy art in peace and quiet: take a look at the collection of medieval art in the Upper Belvedere, where you will also see some equally breathtaking exhibits, but without being carried along by the crowd! As for the culinary delights: Tafelspitz is over-rated in my opinion, but whatever you do, try the 'Wiener gemischten Satz', which is a white wine made from different grape varieties that are also grown together in one vineyard – in contrast to cuvée. ■

## Expert in Interview

► **PROF. KARL LHOTTA**  
President ASN



# ERA-EDTA Working Group on Chronic Kidney Disease and Mineral Bone Disorder (CKD-MBD)

The increasing awareness among the nephrology community of the relevance of disturbances in mineral metabolism, bone disease, and several homeostatic mechanisms that govern its regulation, has led to a boost in research in recent years and may result in changes in everyday practice and clinical outcomes for CKD and post-transplant patients. To

that end, an ERA-EDTA Working Group dedicated to CKD-MBD was established in 2013. The Working Group has launched many inspiring initiatives and projects (e.g. the calciphylaxis registry, or the bone biopsy registry), and is currently organizing several annual meetings focusing on educational themes and research proposals.



Current chairman of the working group is **Mario Cozzolino, Italy**

Find more information at [www.era-edtaworkinggroups.org/en-US/group/ckd-mbd](http://www.era-edtaworkinggroups.org/en-US/group/ckd-mbd)



**MARC VERVLOET**  
Amsterdam, The Netherlands

## Will $\alpha$ -Klotho and FGF23 make you change your clinical practice?

*Current evidence may give a different answer for  $\alpha$ -Klotho and FGF23*

Given the similarity of animal models with genetically modulated expression of genes that encode for either FGF23 or  $\alpha$ -Klotho, and the fact that both proteins in conjunction are involved in phosphate homeostasis, these two compounds are frequently discussed in parallel. The assumption that both factors are required for their biological actions has fuelled the search for ectopic expression of both, but especially for  $\alpha$ -Klotho.

In the last few years FGF23 and  $\alpha$ -Klotho have diverged. An increasing number of studies report interference of both factors on several biological systems independently from each other. Moreover, therapeutic approaches to modify either FGF23 or  $\alpha$ -Klotho probably differ substantially. For these reasons, the question in the title might have a different answer for FGF23 and  $\alpha$ -Klotho. FGF23 has an acknowledged position at center stage of phosphate homeostasis. Given its consistent association with dismal outcome in epidemiologic studies, there is a widespread assumption that, by reducing phosphate concentration or phosphate exposure, a risk reduction can be accomplished that is mediated by a decline in FGF23. It is likely that these novel insights may have already changed clinical practice by raising awareness of maladaptive changes (a compensatory rise in FGF23) that antedate overt hyperphosphatemia, and causing action to be taken accordingly.

Advocates of early use of dietary measures, or even the use of phosphate binder therapy in the absence of hyperphosphatemia, favor this line of reasoning. Indeed in earlier stages of chronic kidney disease (CKD) in particular, the relative risk attributable to rather small increments of FGF23 appears high. This is of importance, because one could argue that primary prevention could be more effective than late intervention when clinical events have already occurred, and reversibility of autonomous FGF23 production in late-stage CKD may be limited. Data that prove this concept are, however, lacking. Moreover, the ability to induce a clinically relevant decline in FGF23 by the use of phosphate binders or other means of limiting phosphate exposure is still debated and the focus of current prospective trials. When considering off-la-

bel use of phosphate binders, one also has to weigh known and currently unrecognized side effects of these compounds.

In recent years, the perspective on FGF23 has changed in at least two aspects: factors that dictate its levels and organ systems beyond the kidney that are being influenced by FGF23. The recognition that a wide range of factors besides phosphate dictates its level holds the promise of additional options to lower FGF23. Among these other factors are calcium, iron deficiency and parathyroid hormone (PTH). A recent secondary analysis of the EVOLVE trial (a placebo-controlled clinical trial examining improvements in clinical endpoints by cinacalcet in hemodialysis patients) demonstrated a surprisingly steep decline of FGF23. Even more intriguing was the observation that reduction in FGF23 was associated with improvement of the primary composite endpoint of the EVOLVE trial and several components which formed this composite. So interestingly, like the concept that phosphate-controlling interventions may need to target FGF23 and not phosphate, the hypothesis emerges that the efficacy of PTH-lowering treatment should be judged on its FGF23-lowering potential. In turn, one could argue that failing to lower FGF23 renders cinacalcet futile. There is no question, however, that these provocative theories require prospective testing.

The other change in perspective on FGF23, besides the recognition of other factors than phosphate dictating its level, is that many systems other than mineral metabolism are under the influence of this bone-derived phosphaturic hormone. The best example is the  $\alpha$ -Klotho-independent pathologic effect on cardiomyocyte ultrastructure and myocardial geometry and function. These findings connect strong epidemiologic data between heart disease and FGF23 to structural abnormalities. These novel insights are currently difficult to translate into changes in everyday clinical practice. There are, however, a few exceptional findings that may actually lead to change in treatment pattern. A large study in non-CKD patients with stable ischemic heart disease not only confirmed the dismal prognostic meaning of high FGF23 levels, but importantly also found that FGF23 very convincingly identified subjects that could benefit the most from angiotensin-converting enzyme (ACE)-inhibitor therapy. As such FGF23 might assist in tailored treatment for those at highest risk.

Most recently, an important new expansion of the pathologic influence of FGF23 was shown. A somewhat neglected is-

sue in nephrology, and especially in CKD-mineral and bone disorders (CKD-MBD) research, is the fact that non-cardiovascular mortality has a higher incidence than cardiovascular death. To a large extent, this is ascribed to infections. In light of this, the finding that FGF23 itself directly, and  $\alpha$ -Klotho-independently, suppresses host defense by interfering with neutrophil function is an eye-opener [2]. This important finding bridges two systems, which so far had hardly any connection: hormonal mineral regulation and the immune system. From a clinical perspective, this underscores the hypothesis that FGF23 should be a target of treatment. One important hurdle to more widespread clinical determination of FGF23 is the assay itself. Different clinical conditions have a different impact on FGF23 cleavage. Sampling handling and storage condition may be critical, and finally currently used enzyme-linked immunosorbent assays (ELISA) are rather expensive.

Compared with FGF23,  $\alpha$ -Klotho will less likely influence everyday clinical practice soon. However, the number of organ systems and the magnitude of pathology inflicted by CKD-induced  $\alpha$ -Klotho deficiency are arguably even more impressive than for FGF23. Vascular and other ectopic calcification, myocardial hypertrophy, podocytopathy, endothelial cell function, immune function and many other metabolic pathways suffer a lack of this most intriguing circulating compound.

Several puzzling observations, however, persist. Although  $\alpha$ -Klotho concentration does indeed decline with CKD, its level remains substantial even in dialysis-dependent kidney disease, although a recently described semi-quantitative method did find a linear decline with advancing CKD. Evidence of relevant ectopic production that may account for this residual  $\alpha$ -Klotho is lacking. Moreover, animal studies demonstrate that the kidney is virtually the exclusive source of  $\alpha$ -Klotho. This, however, does not exclude the possibility that after long-term CKD some tissues could contribute to the circulating pool of soluble Klotho.

In contrast to FGF23, epidemiologic studies are not consistent in demonstrating an association between  $\alpha$ -Klotho and clinical outcome. These studies, however, require careful interpretation because uncertainty exists about the validity of the ELISAs used, especially when applied in the urine. A final and most critical barrier to widespread implementation of  $\alpha$ -Klotho measurement into clinical practice, is that it is currently unknown if increasing its level improves any clinical

outcome, and moreover therapeutic measures to accomplish an increase are unknown. Despite the presence of a vitamin D-responsive element in the Klotho gene and encouraging results from animal studies, vitamin D has not been shown to increase  $\alpha$ -Klotho in human patients. Also cinacalcet and anti-oxidant treatment failed to improve  $\alpha$ -Klotho concentrations. In albuminuric diabetic patients with normal estimated glomerular filtration rate (eGFR) use of an angiotensin receptor blocker (ARB) did induce a modest increase of  $\alpha$ -Klotho. It is

unknown if diseased kidneys with reduced GFR can increase Klotho production through this treatment. Recent interesting observations from endocrinology reveal a possible role of growth hormone or IGF-1 in Klotho production.

In conclusion, FGF23 appears to be close to more widespread clinical application. Key information from clinical studies, however, should ideally be awaited, mainly to answer the question whether substantial reductions of FGF23 can be accom-

plished, and if that brings any benefit. For  $\alpha$ -Klotho, more even fundamental steps are required before a clinical application can be envisioned. ■

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**MARIO COZZOLINO**  
Milan, Italy

Traditional risk factors have proven associations with cardiovascular (CV) mortality in chronic kidney disease (CKD). These include smoking, dyslipidemia, diabetes and left-ventricular hypertrophy. However, there is a growing body of evidence supporting the role of other risk factors that induce CV events through various mechanisms, especially vascular calcification. These 'novel' risk factors include inflammation, and altered calcium and phosphate metabolism. Abnormal calcification is a prominent complication in CKD. Eye disease, necrotic skin lesions, atherosclerosis and soft-tissue deposition have calcification as a central feature. Among all of the pathophysiologic mechanisms in CKD, vascular calcification is strongly associated with CV mortality. It appears that abnormal bone metabolism is the most likely culprit behind vascular calcification.

Bone metabolism can either be increased or decreased in CKD. Decreased bone metabolism in adynamic bone disease means a loss of buffer capacity for peak calcium and phosphate exposure. Thus, either calcium or phosphate levels can fluctuate, disrupting homeostasis. On the other hand, hyperdynamic bone can be a source of excess calcium and phosphate, which are eventually deposited in various areas in the body. Bone can be directly and actively involved in CV disease. Bone has been shown to produce  $\alpha$ -Klotho and fibroblast growth factor 23 (FGF23).  $\alpha$ -Klotho decreases parathyroid hormone (PTH). It also has FGF23-independent effects (anti-calcifying, antioxidant, vasoprotective and decreasing phosphate levels through phosphaturia). FGF23, on the other hand, has a direct effect on the myocardium, increasing left-ventricular hypertrophy. In early stages of CKD, the rise in FGF23 levels occurs earlier than increases in phosphate or PTH levels; hence, FGF23 has been proposed as an early biomarker of disordered phosphorus metabolism. In later stages of CKD, FGF23 dramatically increases, along with

## Abnormal bone metabolism: the most likely culprit for vascular calcification

*Hyperphosphatemia as a novel risk factor for mortality in chronic kidney disease*

phosphate and PTH levels, eventually peaking during dialysis. These rapid elevations in FGF23 are correlated with further left-ventricular hypertrophy.

Hyperphosphatemia per se precipitates vascular calcification and endothelial dysfunction. The exposure of vascular smooth muscle to phosphate in vitro transforms these muscle cells into osteoblasts and osteochondrogenic cells. When combined with the ventricular hypertrophy induced by FGF23, the risk for CV events increases. When looking at survival rates, phosphate also exhibits a dose-response relationship, with the best survival occurring in those with phosphate below target levels. Together, phosphate and FGF23 levels rise and fall depending on the glomerular filtration rate and dialysis treatment. Worsening kidney disease is related to increasing serum FGF23 and phosphate levels.

Previously, PTH was seen as the primary influence behind calcium, vitamin D and phosphate metabolism. However, understanding of the role of phosphate in bone metabolism has changed. On its own, phosphate directly increases PTH, with continued exposure to phosphate leading to stimulation of parathyroid cell growth. It is becoming clearer that phosphate is the driving force behind overall bone metabolism, becoming the central issue in CKD and its associated bone and mineral disease. In light of these findings, the 3Ps hypothesis for CKD was developed. This hypothesis deals with major risk factors for CV mortality in CKD as part of a single pathogenic process. The three Ps are: blood Pressure, Proteinuria and Phosphate. This framework has been verified in animal studies, and human studies on the 3Ps are ongoing.

With these 3Ps present in patients with CKD, along with elevated calcium levels, a 'perfect storm' of risk factors causes accelerated calcification. These risk factors push vascular smooth cells to transform into calcium-producing cells (essentially osteoblasts). Metabolic goals should be geared towards the reduction of CV mortality in CKD. These goals are the reduction of dietary phosphate intake, serum phosphate, PTH and FGF23.

With multiple options available for the reduction of phosphate, focus has been on agents that do not contain calcium. This is because it is thought that calcium itself functions as a substrate for calcification. Several factors influence the choice of phosphate binder for patients, including older age, male sex, postmenopause, diabetes, low bone turnover, vascular / valvular calcification and inflammation.

Unlike calcium-based phosphate binders, non-calcium-based phosphate binders, such as lanthanum carbonate, have been able to reduce the progression of bone disease to adynamic bone among patients with CKD. Importantly, data from the Current Management of Secondary Hyperparathyroidism: A Multicentre Observational Study (COSMO) study in CKD patients on dialysis demonstrated that the use of phosphate-binding agents, compared with no phosphate-binding agents, was associated with a lower risk of all-cause and CV mortality. Interestingly, a meta-analysis demonstrated that the use of non-calcium-based phosphate binders resulted in a 22% reduction in all-cause mortality in patients with CKD (risk ratio 0.78, 95% CI 0.61, 0.98).

In summary, new evidence suggests that the bone has a more central role in CKD than previously believed. One of the ways bone influences outcomes in CKD is through the production of FGF23 and phosphate. Levels of these two substances are directly proportional to CV events and survival. FGF23 heralds the increase in phosphate and may be an early marker for bone disease in CKD. The use of non-calcium-based phosphate binders is associated with a lower mortality risk compared with calcium-based phosphate binders. ■

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## Cappuccino with Claudio Ronco

Take a break and enjoy a cappuccino while watching a video of Professor Claudio Ronco on [www.youtube.com](http://www.youtube.com)

The attendees of the 53rd ERA-EDTA Congress are invited to join his "Cappuccino with Claudio Ronco" series on Youtube (enter "Cappuccino with Claudio Ronco" into the search mask on Youtube). In his short films Professor Ronco discusses new topics with other experts.

**Fresh videos will be available tonight!**



# Is there an ideal biomarker of bone metabolism in CKD?

We need to better understand the predictive diagnostic value of biomarkers in CKD-MBD



**PABLO UREÑA-TORRES**  
Paris, France

Progressive chronic kidney disease (CKD) ineluctably leads to mineral and bone disorders (MBD). The numerous biochemical alterations observed in CKD – namely reduced natural and active vitamin D metabolites, hypocalcemia, hyperphosphatemia, high parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), sclerostin, and low Klotho – independently or in concert affect CKD mineral and bone metabolism (CKD-MBD) and ultimately bone quality and quantity. Moreover, a significant number of medications aimed at controlling or normalizing these biological alterations often directly or indirectly impact bone metabolism; such medications include calcium salts, intestinal phosphate binders, vitamin D compounds, calcimimetics, bisphosphonates, and other emerging therapies.

The usual circulating biomarkers of bone metabolism, either alone or combined, are poor predictors of the type of renal osteodystrophy (ROD) in CKD-MBD. Thus, to establish a firm diagnosis of the type of bone disease in CKD, the qualitative and quantitative histomorphometric evaluation of a bone biopsy still remains the gold standard. The bone histomorphometric nomenclature system describes essentially five types

of ROD in CKD: osteitis fibrosa or high bone turnover; adynamic bone disease; osteomalacia; mixed lesions associating high bone turnover and osteomalacia; and osteopathies due to trace metal overload (aluminum, fluoride, strontium). This classification of CKD-MBD is mainly based on three parameters: bone formation rate (BFR) after tetracycline double labeling, bone volume, and the amount of unmineralized osteoid surface, or in other words the presence or absence of mineralization defect.

As an example (Figure 1), patients with an increased number of unmineralized osteoid surfaces, low number of osteoblast and osteoclast cells, and a decreased BFR are classified as having osteomalacia. In secondary hyperparathyroidism (SHPT) with severe osteitis fibrosa, the chronic and marked excess of PTH leads to marrow fibrosis, expansion of osteoid surfaces, woven osteoid, increased number and activity of osteoblasts, numerous osteoclasts and resorptive surfaces. Tetracycline labels cover the majority of the bone mineralization surfaces and a larger space between the double-labeled staining indicating accelerated BFR. No mineralization defect is observed. In adynamic bone disease there is scanty or the absence of tetracycline labeling along the bone surface. There is a very low number of osteoblast and osteoclast cells. Low bone turnover is represented by the absence of differentiation between the double-tetracycline labeling.

Unfortunately, bone biopsy is still rarely indicated and performed in CKD patients, probably because of difficulties in finding experienced teams and appropriate facilities to analyze them. There is also the perception that bone biopsy is an invasive and painful procedure. Thus considerable efforts have been devoted to the search for reliable, noninvasive biomarkers of bone metabolism in CKD patients. These biomarkers of bone turnover in CKD-MBD would be of great importance in recognizing specific conditions, identifying

patients at risk, and guiding patient-tailored therapeutic intervention.

Two molecules, vitamin D and PTH are generally not considered as biomarkers of bone metabolism, but they are probably the most important regulators of bone turnover and bone mineralization. In the French cohort NephroTest™, including more than 1,000 CKD patients, we found that 80% of patients with CKD stages 3-5 were vitamin D deficient (25OHD <15 ng/ml) or insufficient (25OHD 15–13 ng/ml), and only 20% had normal vitamin D status [1]. Low circulating 25OHD levels (<10–15 ng/ml) are widely recognized to be associated with rickets in children and osteomalacia in adults. Such bone mineralization defects can lead to skeletal deformities and spontaneous bone fractures.

PTH is the principal molecule controlling bone remodeling. Intermittent physiologic doses of PTH increase bone formation and bone mass; however, extremely and constantly high or low PTH results in bone loss, increased risk of skeletal fractures and mortality. Regardless of the type of assay, PTH values show a relative good correlation with BFR and with most of histomorphometric parameters. However, approximately 30% of dialysis patients with normal/low BFR show PTH values between 200 and 600 pg/ml, or 2-9 fold the upper limit of the reference value. In spite of these findings, PTH, measured by second- and third-generation assays, is the most used and useful biomarker in the diagnosis of ROD. However, one should keep in mind that PTH mostly reflects the degree of parathyroid activity and to some extent the degree of bone turnover. PTH is not always well correlated with BFR.

Bone is composed of cells: 10% osteoblasts and osteoclasts, and 90% osteocytes. There is also extracellular matrix: 77% inorganic, mostly in the form of hydroxyapatite, and 23% organic matrix, mostly type I collagen (85%) and non-collagenous proteins (15%). Analyzing the metabolism of these proteins could be a useful tool in the assessment of ROD. However, the results of several studies investigating the utility of type I collagen-related molecules, either associated with bone formation (PINP and PICP) or bone resorption (NTX, CTX, PYD, DPD), have been inconclusive and require validation by larger studies [2].

Among the non-collagenous proteins, bone-specific alkaline phosphatase (BSAP) can be considered as the most useful bone biomarker in the diagnosis of the type of ROD, improving PTH predictive value. Tartrate-resistant acid phosphatase (TRAP5b) emerges as a promising resorption marker, unaffected by renal function and correlating well with bone histomorphometric parameters in dialysis patients. Among the new biomarkers, FGF23 also represents an emerging and interesting possibility. FGF23 levels significantly increase in the circulation of CKD patients at 10 to 15 ml/min of glomerular filtration rate (GFR) earlier than PTH (break-point at 57 ml/min for FGF23 compared to 46 ml/min for PTH). FGF23 is mainly produced by osteocytes and osteoblasts, and exerts its major physiologic actions in the kidney, stimulating urinary phosphate excretion and inhibiting calcitriol synthesis.

For the last ten years it has been suggested that FGF23 could also play an important role in the regulation of bone mineralization. Indeed, if there is the absence of FGF23 (as in FGF23-knockout animals) or if there is an excess of FGF23 (as in Klotho-knockout animals), there is a severe bone mineralization defect. Likewise, high FGF23 values have been associated with reduced osteoid thickness and osteoid maturation time, both in children with normal renal function and in CKD dialysis children. This enigma (*continued on page 8*)

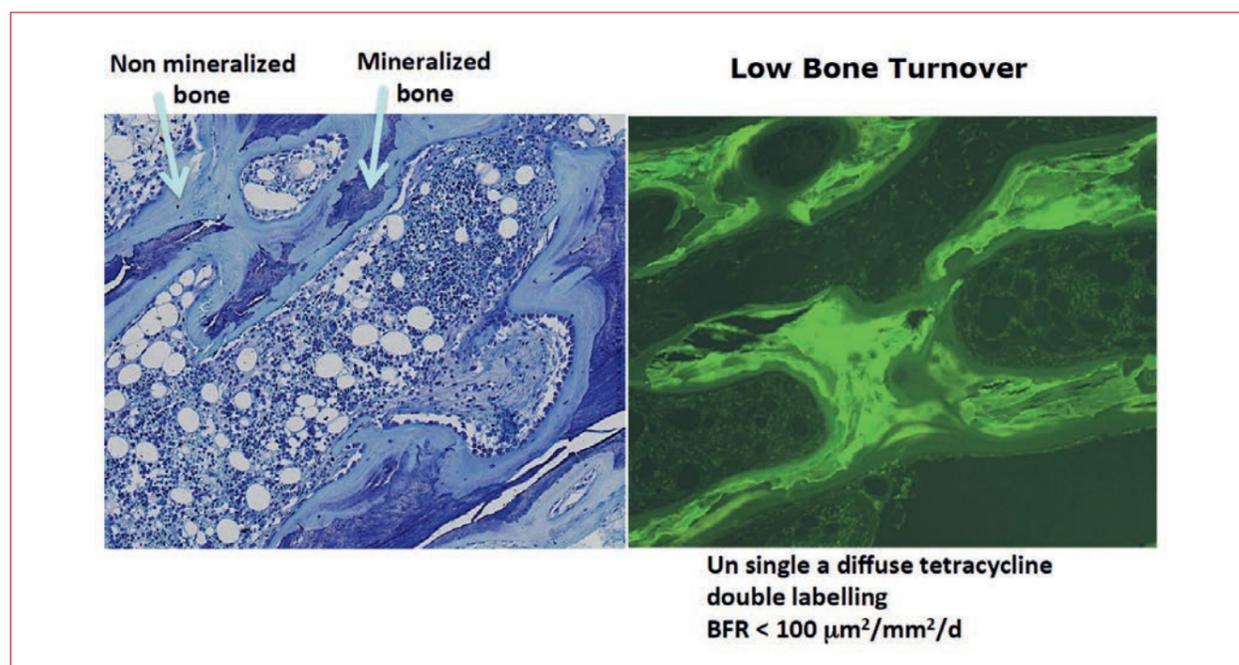


Figure 1: Types of Renal Osteodystrophy © Urena

High Bone Turnover	PTH	Total AP	BSAP	PTH ≥ 200 BSAP ≥ 20
	≥ 200	≥ 200	≥ 20	≥ 20
Sensitivity (%)	72	50	100	100
Specificity (%)	80	90	100	80
PPV (%)	92	94	84	94
NPV (%)	47	36	100	100

Table 1: Plasma BSAP and PTH Levels in Dialysis Patients with Low and High Bone Turnover

© Urena

BSAP equal or higher than 20 ng/ml, alone or combined with PTH of 200 pg/ml, had the highest sensitivity, specificity, and predictability values for the diagnosis of high turnover bone disease.

# Rare Disease Expert Forum

Advancing the Management  
of Rare Diseases

## Rare Renal Diseases Are Growing Up Lunch Symposium at the 53<sup>rd</sup> ERA-EDTA Congress

Chaired by Prof. Rainer Oberbauer, Vienna

We are delighted to invite you to participate in the satellite symposium  
**Rare Renal Diseases Are Growing Up,**  
An eminent pan-European panel of experts will offer insights into the  
contemporary management and care of patients with rare renal tubulopathies.

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

**Monday, May 23<sup>rd</sup>, 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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# PTH metabolism and signaling in CKD: focus on PTH resistance

*New insights into the pathogenesis of chronic kidney disease–mineral bone disorder*



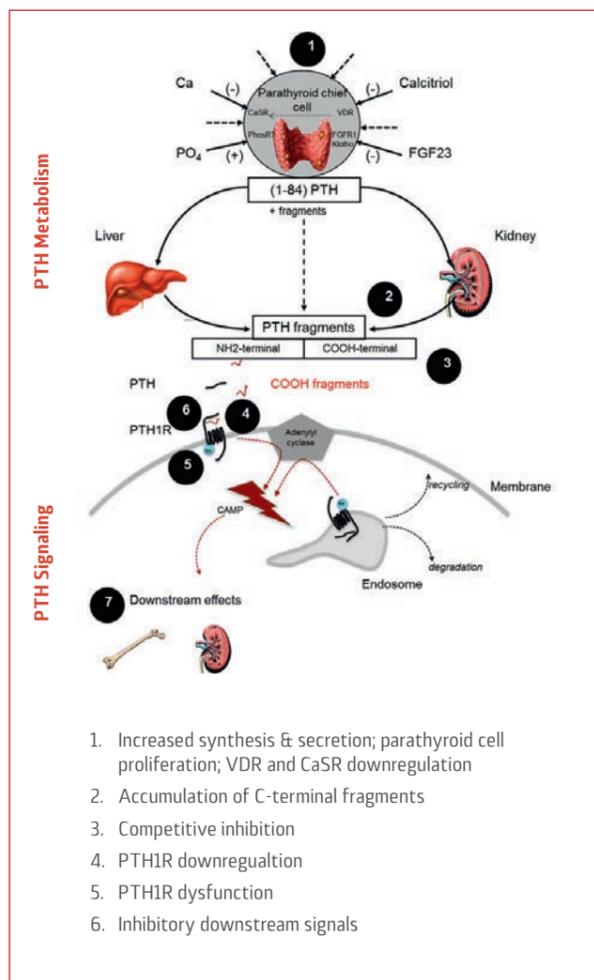
**PIETER EVENEPOEL**  
Leuven, Belgium

Chronic kidney disease - mineral bone disorder (CKD-MBD) is a systemic disorder that describes the complex bone and mineral abnormalities that occur in CKD. Secondary hyperparathyroidism (HPT) is an integral component of CKD-MBD and, if left unchecked, leads to a worsening of laboratory abnormalities, bone disease, and calcification. In recent years, insights in the pathogenesis of secondary HPT have grown and the therapeutic armamentarium to tackle this condition has expanded substantially.

Although sustained increases in PTH secretion in individuals with normal kidney function result in elevated serum calcium, 1,25-dihydroxyvitamin D, and FGF-23 levels, secondary HPT in patients with end-stage renal disease is associated with a markedly different phenotype. These individuals display a wide range of serum calcium concentrations, increased serum phosphate, and markedly elevated FGF-23 values in conjunction with very low 1,25-dihydroxyvitamin D levels. Bone metabolism also differs substantially; in contrast to the increased osteoblastic and osteoclastic activity observed with increased PTH levels in individuals with normal renal function, the skeleton in the uremic milieu shows a more heterogeneous picture. Of note, low bone turnover disease is the most prevalent bone condition in patients with ESRD, despite these patients presenting PTH levels several fold above the upper normal limit.

Both altered PTH metabolism and posttranslational modifications of PTH and PTH resistance may contribute to the complex relationship between circulating PTH levels and outcomes in CKD. In CKD, increases in circulating PTH levels are not necessarily paralleled by increased PTH signaling. A disturbed PTH metabolism in CKD results in a marked prolongation of the half-life of C-terminal PTH fragments in the circulation and their accumulation in the extracellular space. It is increasingly recognized that C-terminal PTH fragments exert biologic effects that are distinct if not opposite to bioactive PTH.

Whether posttranslational modifications of PTH (e.g. oxidation, glycation, carbamylation) do occur in vivo to a relevant extent remains a matter of ongoing debate. Less controversial is the issue of **PTH resistance**. Already 50 years ago, Evanson reported that the calcemic response to an infusion of parathyroid extract was significantly less in hypocalcemic patients with renal failure than in patients with hypoparathyroidism and normal renal function. In a subsequent landmark study, Massry et al. studied the effects of an infusion of parathyroid extract on the serum calcium and urinary phosphate levels in 105 individuals (normal persons and patients across all stages of CKD). The calcemic response was significantly lower in CKD patients, and phosphaturia could only be induced in normal persons and patients with mild-to-moderate renal failure.



**Figure 1: PTH Metabolism and Signaling in CKD** © Evenepoel

Although the phenomenon of resistance to PTH has long been recognized, factors contributing to its development remain elusive. Phosphorus loading and calcitriol deficiency, both common in the setting of advanced CKD, have been implicated in the pathogenesis of PTH resistance, but underlying molecular mechanisms remained obscure. Recent evidence identified decreased PTH1R expression (mediated by oxidative stress) and inhibitory downstream signals (mediated by sclerostin and osteoprotegerin) as mechanisms underlying PTH resistance in CKD. Impaired PTH signaling may be as detrimental as increased PTH signaling.

Defining the optimal PTH range is thus of utmost importance. The altered PTH metabolism and the phenomenon of PTH resistance in CKD, along with the important analytical and biological variability of PTH, render this quite a challenge. While defining the optimal PTH range may be achievable at the population level, it may prove an almost impossible task at the individual level. This is a disillusioning thought in an era of personalized medicine. Some even advocate that the time has come to abandon PTH as an outcome biomarker and target of therapy in CKD. After all, PTH is more reflective of parathyroid activity than of bone remodeling and related morbidity/mortality.

A functional and readily available assay reliably quantifying PTH1R signaling tone or sensitivity would be a great step forward. Such an assay will allow the optimization of tissue (bone / vascular) PTH1R signaling tone and function in order to maintain bone and arterial structure in CKD and other conditions such as diabetes and aging. Parallel to the development of such an assay, the performance of more specific biomarkers (or panel of biomarkers) should be further explored against the gold standard, i.e. a bone biopsy. Since these biomarkers are not free of limitations (renal clearance and metabolism, high biological variability), a bone biopsy may still be needed in some conditions. Recent technical advances have reduced the morbidity of and may help to further lower the threshold for performing this diagnostic procedure. ■

(continued from page 6) appears to be deciphered in a recent publication, which demonstrates that FGF23 modulates bone mineralization by regulating tissue non-specific alkaline phosphatase (TNAP), specifically through FGFR3 and independently of Klotho. FGF23 inhibits TNAP and, in this way increases extracellular concentration of pyrophosphate, reduces the amount of inorganic (free) phosphate, and indirectly stimulates osteopontin gene expression, a known mineralization inhibitor [3].

In conclusion, in the absence of bone biopsy, it appears that there is no ideal biomarker of bone metabolism in CKD-MBD. Further studies, based on bone histomorphometry, are clearly needed to better understand the predictive diagnostic value of old and new, alone or combined, biomarkers of bone metabolism in CKD-MBD. ■

## References

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## Session

**CKD-MBD/CME 10**

**New insights into CKD-MBD**

**TODAY, 13.15–16.30  
HALL F**

## Expert in Interview

► **PROF. PIETER EVENEPOEL**



## DESCARTES – an official ERA-EDTA Working Group

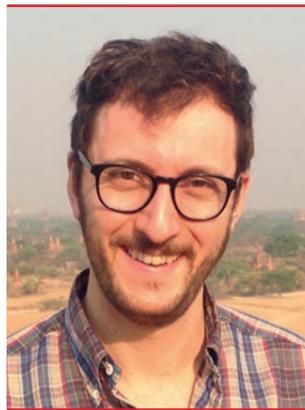


Current chairman of the working group is **Daniel Abramowicz, Belgium**

Find more information at [www.era-edtaworkinggroups.org/en-US/group/descartes](http://www.era-edtaworkinggroups.org/en-US/group/descartes)

The DESCARTES Working Group ("Developing Education Science and Care for Renal Transplantation in European States") is dedicated to renal transplantation. Its major objective is to set up clinical trials that focus on unambiguous, meaningful clinical endpoints, including estimates of cost and cost-effectiveness, that have a suf-

ficiently long follow-up time and which enroll patients who are usually excluded from industry-driven clinical trials. The idea is to establish a network of clinical trial sites for future translational research projects. In addition to that, the Working Group also organizes regular CME courses.



**JULIEN COUSSEMENT**  
Brussels, Belgium

## Should we treat asymptomatic bacteriuria after renal transplantation?

Infections remain a major cause of morbidity and mortality in the modern kidney transplantation era. Symptomatic urinary tract infection (UTI), which is defined as the association of a positive urine culture with the presence of symptoms and/or signs referable to UTI, is the most common infection in this population. As a consequence, UTI is the primary reason for antibiotic use in kidney transplant recipients.

In a time of increasing resistance to antimicrobial agents and rising health-related costs, factors that trigger UTIs need to be understood, and if possible prevented. Whether asymptomatic bacteriuria (which is generally defined as bacteriuria without signs or symptoms of UTI) is a modifiable risk factor for symptomatic episodes, and should therefore be screened for and treated, remains controversial. However, screening for and treating asymptomatic bacteriuria is an old habit in many kidney transplantation units, where asymptomatic bacteriuria is a common finding. This strategy was often initiated before the emergence of evidence-based transplantation. A number of factors fed that habit, including the fact that graft denervation impedes kidney pain, the alteration of inflammatory signs by the

immunosuppressive agents, and the fear that rapidly progressing infections can occur in immunosuppressed patients.

However, no study has demonstrated a clear benefit from treating asymptomatic bacteriuria with antibiotics in kidney transplant recipients. With the support of the Cochrane Kidney and Transplant Group, we performed a systematic review and meta-analysis to assess the benefits and harms of using antimicrobial agents in this situation. Two controlled studies (200 patients) comparing antibiotics versus no therapy were included in our systematic review. Based on these two trials, treating kidney transplant recipients with asymptomatic bacteriuria has uncertain effects on preventing symptomatic UTI, and entails indeterminate risks for selecting resistant strains. Our group is currently performing a randomized, parallel-group, multicenter, open-label, superiority trial comparing antibiotics versus no therapy in order to determine if antibiotic treatment reduces the incidence of a first episode of symptomatic urinary tract infection in kidney transplant recipients with asymptomatic bacteriuria. Fifteen hospitals from France and Belgium are collaborating in this trial, called the 'BiRT Study', with the aim of including 198 patients, half of them randomized to antibiotic therapy (10 days, started and selected according to the antibiogram results) and half to no treatment.

These clinical trials should be correlated with molecular studies focusing on the role of host-pathogen interactions

in the urinary tract. In immunocompetent patients, many virulence factors are now well described in pathogens such as *E. coli*, including adhesins, toxins and nutrient acquisition factors. The role of these factors after kidney transplantation has not been well studied. However, it would be of great interest to identify some bacterial factors that promote detrimental outcomes such as acute graft pyelonephritis and kidney graft failure. Using next-generation sequencing, we are collaborating with the group of James R. Johnson (Minneapolis, USA) to compare the presence of bacterial virulence factors of *E. coli* isolated from asymptomatic bacteriuria after renal transplantation to the molecular profile of *E. coli* recovered during acute graft pyelonephritis. Interestingly, our preliminary results suggested that pap genes (which code for P fimbriae) are more commonly identified in graft pyelonephritis-associated isolates than in those associated with asymptomatic bacteriuria. This could indicate that bacterial virulence factors play a role in kidney transplant recipients with bacteriuria, and that not all bacteriuric episodes should be managed the same way.

As a conclusion, asymptomatic bacteriuria is common after renal transplantation. Before breaking with the old habit of treating asymptomatic bacteriuria, we believe that more evidence is required. It is to be welcomed that several studies, including three prospective trials comparing antibiotics to no treatment in kidney transplant recipients with asymptomatic bacteriuria, are currently underway to address this question. ■

## Thrombotic microangiopathy in kidney allograft: how to proceed?

*Eculizumab improves the prognosis of kidney transplant recipients with aHUS in their native kidneys*

The occurrence of thrombotic microangiopathy (TMA) after kidney transplantation prompts two main steps: first, differential diagnosis and, second, therapeutic management. With regard to differential diagnosis, the main etiologies to be investigated are recurrence of atypical hemolytic uremic syndrome (aHUS), nephrotoxicity of calcineurin-inhibitors (CNIs) or less frequently mammalian target of rapamycin (mTOR) inhibitors, vascular lesions associated with severe, acute, clinical antibody-mediated rejection and, less often, viruses such as cytomegalovirus or parvovirus B19. Differential diagnosis therefore relies on past history of native kidney disease, elevated trough levels of CNIs, renal biopsy or viral PCRs.

The most frequent cause of post-transplantation TMA is CNI-nephrotoxicity, which will require either dose adjustment or conversion to a non-nephrotoxic drug such as belatacept. In this presentation, we will focus on the recurrence of aHUS after kidney transplantation. aHUS very frequently recurs after kidney transplantation (in about 70 to 80% of cases). As a consequence, graft survival is poor (around 30% at 5 years) and is correlated with genetic mutations (high risk in the case of mutations in factor H, C3, B; lower risk in other abnormalities). Conventional therapy (plasma exchange) is at best partially effective. aHUS is a chronic disease characterized by uncontrolled activation of the alternative pathway of activation of complement. Eculizumab is a



**CHRISTOPHE LEGENDRE**  
Paris, France

monoclonal antibody directed against the C5 component of the alternative pathway.

In pivotal trials, eculizumab has proved to be efficacious and safe in transplanted patients either with very active disease or with disease partially controlled by long-term plasma exchange. However, for as yet not-well (*continued on page 10*)

(continued from page 9) defined reasons, renal improvement was less impressive in transplanted patients than in patients with aHUS in their native kidneys.

It is therefore possible to use eculizumab when recurrence of aHUS is diagnosed, but it is also possible and probably more useful to prevent aHUS recurrence by early initiation of eculizumab. In published reports as well in our own group's experience, this approach will lead to complete prevention of clinical recurrence and therefore to excellent renal function. So far, safety has been good as long as patients are vaccinated against meningococcus and also receive daily antibiotics. The use of eculizumab could also be useful in patients with aHUS and high immunization against HLA antigens.

Eculizumab has led to a tremendous improvement in the prognosis of kidney transplant recipients with aHUS in their native kidneys. Monitoring and optimal duration of treatment are still a matter of discussion. ■

## An accurate pretransplant urologic workup is essential

*Transplantation into an abnormal lower urinary tract: what should the nephrologist know?*



**LICJA PERUZZI**  
Turin, Italy

the more complex cases that often require bladder diversions or augmentation there is still considerable controversy over the best approach and timing of reconstructive surgery, and no guidelines or clear-cut criteria for indications and timing of surgery are available.

There is undoubtedly an increased risk of complications, mainly urinary tract infection (UTI), eventually leading to graft loss; therefore optimal personalized urologic workup should be undertaken for each patient. The main objective of the urologic workup is to ensure a sterile bladder able to work as an efficient reservoir, with large capacity, high compliance, low pressure and proper ureteral drainage. The bladder must in effect be able to store a sufficient amount of urine at low pressure, with a competent sphincter system and safe mechanism to ensure complete voiding via either spontaneous micturition or intermittent autocatheterization. Pretransplant assessment of the bladder is based on urodynamic evaluation to estimate its capacity, compliance and voiding pressures. This evaluation might be inaccurate in oliguric or anuric children, as well as in adults on dialysis. In these cases, voiding cystourethrography is advisable for definitive anatomic definition of an eventual inadequate system.

This thorough urologic workup is fundamental in order to distinguish between anatomic and functional obstruction (for example, detrusor sphincter dyssynergia or nonrelaxing urethral sphincter obstruction as seen in meningomyelocele) for a surgical or conservative approach. Urine storage and

Obstructive uropathies and other lower urinary tract abnormalities, including neurologic bladder, primary vesicoureteric reflux (VUR) and other malformative complex syndromes, account for over 25% of the causes of chronic renal failure requiring renal replacement therapy in the pediatric age group. Adult patients presenting with an abnormal lower urinary tract are much less frequent (about 5%), and may suffer from a milder form of uropathy with slower progression, be candidates for retransplantation after a failed graft in severe uropathies, or experience posttraumatic or post-malignancy bladder or urethral damage. If in the past concerns were raised over the suitability of renal transplantation in patients with an abnormal lower urinary tract, recent re-evaluation of long-term series shows results comparable with those in other renal transplant recipients. However, in

### Session

**DESCARTES / CME 2**

### Practical issues in kidney transplantation

**TODAY, 09.00 – 12.15  
HALL F**

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**53<sup>rd</sup> CONGRESS**  
**ERA-EDTA**  
MAY 21<sup>st</sup>-24<sup>th</sup> 2016  
**VIENNA AUSTRIA**

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# RUN FOR KIDNEYS

22<sup>ND</sup> MAY 2016 VIENNA

**We are part of!**  
Donation campaign for

**2016**



The Organizing Committee is very pleased to announce the fifth ERA-EDTA Renal Run that from this year will be named **RUN for KIDNEYS** which will take place on **May 22nd at 15.00 during the Vienna Congress**.

Participants will be divided into categories according to age and gender.

The registration fee is € 20,00, pre-registrations must be done **online** for administrative purposes **no later than Saturday, May 15, 2016**.

Cash payment will be provided at the onsite registration desks only.

Onsite registrations will be available at the Registration Area, Level 0 of the congress venue with following opening times:

**Friday, May 20 - 11.00-19.00**

**Saturday, May 21 - 07.00-19.00**

**Sunday, May 22 - 07.00-13.00**

**The Run for Kidneys 2016 proceeds will be donated to MSF (Médecins Sans Frontières).**

Financial help is crucial for MSF to provide life-saving medical humanitarian relief. The ERA-EDTA Council decided to contribute, at least in part, to this important work by raising money during the congress.

We are looking forward to your participation and we are sure you would like to contribute to this charitable activity in supporting MSF.



Photo Laurence Geai



Photo Ton Koene



Photo Ton Koene



Photo Francois Dumont



Photo Nicole Sobacki

**Check the 53<sup>rd</sup> ERA-EDTA Congress official website for further update about the Run for Kidneys 2016!**

voiding at high pressure compromise ureteric drainage and increase the risk of vesicoureteric reflux and graft infections.

Bladder abnormalities due to defunctionalization because of long-term anuria or reduced capacity have a good recovery capacity after diuresis has resumed. However when reduced capacity is due to fibrosis or previous surgery, recovery is less common and reconstruction must be considered. Bladder cycling, although patients do not always comply or consent, can be proposed to identify potentially enlargeable bladders that would not require surgical augmentation.

A bladder that is presumed to be permanently unsuitable for a transplanted kidney can be adequately surgically prepared through improvement of the drainage system (constructing a Mitrofanoff channel from the appendix or a Monti Mitrofanoff small intestine), augmentation (ureterocystoplasty, gastrocystoplasty or enterocystoplasty), or diversion (incontinent or continent catheterizable stoma). This last option is today limited to highly complex situations where no other approach can be envisioned. When enough tissue can be retrieved from a dilated ureter, ureterocystoplasty is the preferred option, in order to avoid exposure of the enteric mucosa to urine, leading to metabolic complications (acidosis or alkalosis according to the enteric segment adopted),

mucus production, urinary stones, infections and potential long-term risk of malignancy. One of the main issues in bladder reconstruction is its timing: before, during, or after the renal transplant. There are no significant differences in outcome, but timing has some implications for the stringency of indications.

Lower urinary tract reconstruction before renal transplantation has the advantage of surgery in advance of immunosuppression. However, it does not spare from surgery those patients whose bladder function will improve with a proper urine flow (as is frequently observed, particularly in small children). Close monitoring of bladder function posttransplantation can be a reasonable option in borderline cases. Reconstruction before transplantation should also take into account the side effects due to anuria. These include accumulation of mucus or acid contents in a 'dry cystoplasty', which might lead to severe irritation, infection, and potentially life-threatening bladder perforation, and the fact that in the long run augmented bladders may decrease in compliance. Pretransplant reconstruction is therefore preferred when the patient has a living donor or has a priority score in the cadaveric organ allocation system to avoid a long stay on the waiting list. Extreme surgical care must be taken during subsequent transplantation to avoid damaging the vascular pedicle of the cystoplasty during ure-

teric reimplantation, the consequence of which is cystoplasty necrosis.

Simultaneous bladder reconstruction with kidney transplantation is not frequently the preferred option. This is because of the risks of delayed wound healing due to high doses of steroids and prolongation of surgical time and postoperative complications that are potentially harmful to the graft. Posttransplant bladder reconstruction allows more stringent indications, limiting surgery to those patients whose bladder capacity does not improve with resumption of urinary flow. This conservative approach may, however, damage the grafted kidney through recurrent UTI in the first posttransplant period. Antibiotic prophylaxis and anticholinergic drugs are often used, particularly in the first 6 months after transplantation, as a complementary treatment to minimize the risk of UTI and bladder overreflexic response.

In conclusion, in a patient with an abnormal urinary tract, an accurate pretransplant urologic workup is necessary to ensure a large, compliant voiding reservoir and eventual augmentation surgery or artificial drainage system. This allows a safe kidney transplant, with long-term outcomes comparable to those in a patient with an unaffected urinary tract, provided that strict observation and urologic followup is maintained posttransplantation. ■

## ERA-EDTA DIABESITY Working Group

The aim of the DIABESITY Working Group is to generate and disseminate knowledge on the nephrological impact of diabetes and obesity. The term 'diabesity' has been coined to describe the concomitant presence of both diseases and their pathogenic association. This represents a major challenge in nephrology, as a considerable proportion of the population with diabesity

may develop complications such as albuminuria, overt proteinuria and decreasing renal function, which if untreated may lead to end-stage renal disease. Importantly, the pathogenetic pathways by which obesity causes renal disease are still unknown. Apart from initiating scientific projects in this field, the Working Group organizes regular CME courses.



Current chairman of the working group is **Carl-Erik Mogensen, Denmark**

Find more information at [www.era-edtaworkinggroups.org/en-US/group/diabesity](http://www.era-edtaworkinggroups.org/en-US/group/diabesity)



**DRAZENKA PONGRAC BARLOVIC**  
Ljubljana, Slovenia

## How should we individualize glycemic control in patients with kidney disease?

*Novel strategies may slow progression of diabetic nephropathy*

Nearly every second patient with type 2 diabetes develops raised albuminuria or a decrease in glomerular filtration rate at a certain point during the course of the disease. Given improvements in cardiovascular survival and increasing prevalence of type 2 diabetes in younger individuals, an even higher prevalence of chronic kidney disease (CKD) is to be expected in the near future. In recent years especially, individualization of glycemic goals and glycemic treatments has been emphasized. However, few tools and few data are available to guide clinicians in deciding on optimal targets and therapeutic choices in individual patients. Nevertheless, one of the most important factors that influences the decision when setting glycemic targets is the presence of CKD.

According to the latest KDIGO guidelines, despite associated confounding factors, glycated hemoglobin (HbA1c) remains

the most appropriate measure for assessing overall glycemic control in CKD. The target level of HbA1c for most patients is set at a value of 7%. There is, however, a special recommendation that the target level could be set higher in patients at increased risk for severe hypoglycemia, which many patients with CKD, especially those with concomitant polymorbid conditions, certainly are. Most importantly, it has never been shown that patients with CKD should have more stringent glycemic control with levels of HbA1c <6.5% or even lower. Interestingly, in the well-known ACCORD study – cited for the increased mortality in the type 2 patients randomized to intensive glucose control (treated to a target HbA1c level of <6.0% compared to <7.5% in the control group) – it was subsequently shown that patients at higher mortality risk in the intensively treated group were those with CKD. Of note, patients at increased risk of mortality were not only those with advanced kidney disease, but also those in CKD stages 1 and 2.

Little is known about the diet that might help normalize blood glucose values and also be renoprotective. Our study

group has designed a special study named CHEF aimed at identifying whether calorie restriction in obese patients at risk for renal disease could help preserve renal function and improve their cardiovascular health. In addition, patients with

## Session

**DIABESITY / CME 5**  
**Diabetes and obesity in renal disease**

**TODAY, 09.00 – 12.15**  
**HALL G**

CKD / stage eGFR (ml / min / 1.73m <sup>2</sup> )	1-2 above 60	3a 60-45	3b 45-30	4 30-15	5 ESRD
metformin	—	—	---	---	---
glibenclamide	—	---	---	---	---
gliquidone	—	---	---	---	---
glipizide	—	---	---	---	---
glimepiride	—	---	---	---	---
gliclazide	—	---	---	---	---
repaglinide	—	---	---	---	---
acarbose	—	---	---	---	---
exenatide	—	---	---	---	---
liraglutide	—	---	---	---	---
sitagliptin	—	---	---	---	---
vildagliptin	—	---	---	---	---
saxagliptin	—	---	---	---	---
linagliptin	—	---	---	---	---
dapagliflozin	—	---	---	---	---
empagliflozin	—	---	---	---	---
canagliflozin	—	---	---	---	---

**Figure 1: Some oral antihyperglycemic agents and their use at different stages of chronic kidney disease**

Legend: full line – no dose adjustment needed; dashed line – dose adjustment may be needed © Pongrac Barlovic

diabetes and kidney disease receive different advice on diet with respect to changes in kidney function, depending on potassium and phosphates levels. The amount and type of physical activity most beneficial for patients at different stages of kidney disease have also not been extensively studied.

Non-pharmacologic treatment is the mainstay of any antihyperglycemic regimen. In patients with CKD, pharmacologic agents to achieve target HbA1c have to be chosen carefully. Metformin, the first-line therapy for patients with type 2 diabetes, is contraindicated when estimated glomerular filtration rate (eGFR) falls below 30 ml / min / 1.73 m<sup>2</sup> and has to be used with caution and in adjusted dose if eGFR is between 45 and 30 ml / min / 1.73 m<sup>2</sup>. Sulphonylureas like glipizide and gliclazide are metabolized in the liver and excreted in urine as inactive or weakly active metabolites, so they

can be used even in patients with advanced kidney disease. Meglitinides are very short-acting insulin secretagogues. Repaglinide, for example, is 90 % transformed to inactive metabolites in the liver and can be used cautiously up to eGFR >30 ml / min / 1.73 m<sup>2</sup>. However, due to the risk of hypoglycemia, it is not suitable for treatment of patients with end-stage renal disease (ESRD). Alpha-glucosidase inhibitors can cause liver failure in patients with CKD, especially when eGFR falls below 30 ml / min / 1.73 m<sup>2</sup>. Thiazolidindiones act mainly by improving insulin resistance and could be beneficial in patients with CKD. They reportedly reduce albuminuria, but cause fluid retention and increase bone fracture risk; pioglitazone has also been linked to a risk of bladder cancer.

In the field of hyperglycemia treatment, several rather exciting new classes of drug have appeared in the last few years. Dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like

peptide 1 (GLP-1) receptor agonists may exert a renoprotective effect by reducing inflammation, fibrosis and blood pressure. During treatment with DPP-4 inhibitors a reduction in albuminuria was observed in patients irrespective of the initial albuminuria level and while receiving stable doses of renin-angiotensin-aldosterone system (RAAS) inhibitors. Perhaps the most interesting new antihyperglycemic drug class are the sodium-glucose cotransporter-2 (SGLT2) inhibitors. They reduce proximal tubular glucose and sodium reabsorption, thereby increasing distal sodium delivery to the macula densa, restoring tubuloglomerular feedback, and afferent arteriole vasoconstriction and decreasing hyperfiltration in animals. In humans, SGLT2 inhibition was recently shown to reduce hyperfiltration in normotensive, normoalbuminuric patients with type 1 diabetes. In clinical trials in type 2 diabetes, SGLT2 inhibition was associated with modest, acute declines in eGFR followed by the maintenance of stable renal function and reduced albuminuria. Simultaneous use of an SGLT-2 inhibitor and RAAS blockade may become an effective strategy to slow progression of diabetic nephropathy.

#### Take home messages

- Control of glycemia and blood pressure are the mainstays to prevent kidney damage and slow its progression in diabetes
- The timing of intensity of antihyperglycemic treatment is crucial, with longstanding positive benefit on kidney function from early institution of intensive glucose control.
- In the field of glucose lowering drugs, there is emerging evidence that some agents may have renoprotective effects that are independent of their glucose-lowering effects. ■

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## Macrophages: their role in diabetic kidney disease

Overcoming current barriers to M2-macrophage cell therapy



**JOSEP CRUZADO**  
Barcelona, Spain

Macrophages are highly heterogeneous cells that are categorized into subpopulations based on their distinct functions. Two well-defined phenotypes are commonly described as classically activated macrophages (M1 macrophages), produced by exposure to lipopolysaccharide (LPS) or interferon gamma (IFN-γ) which are proinflammatory, and alternatively activated macrophages (M2 macrophages) induced by Th2 cytokines such as IL-4 and IL-10. M2 macrophages can be further subcategorized into at least three subgroups: M2a induced by IL-4 and / or IL-13 (reparative); M2b

induced by immune complexes; and regulatory macrophages known as M2c (antiinflammatory macrophages). However, in vitro classification of macrophages does not necessarily reflect their function in vivo.

The pathogenic role of macrophages in acute and chronic kidney disease, as well as in the reparative phase after kidney injury, has been demonstrated by depletion of kidney macrophages by liposomal clodronate. However, this topic is controversial due to macrophage plasticity. Macrophages change their phenotype in response to signals from the local kidney milieu, although the mechanisms by which they are polarized are not well understood. In diabetic kidney disease, some authors postulate that M1 macrophages are involved in the early phase whereas M2 play a role in later stages of the disease. However, other authors suggest that inflammation in chronic nephropathy induces M1 persistence and progressive depletion of antiinflammatory M2 macrophages in renal tissue.

There is evidence showing that modification of the environmental milieu in diabetic kidney disease by several agents such as hepatocyte growth factor is associated with increased numbers of renal *(continued on page 15)*

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**Weight loss reduces proteinuria in obese CKD patients**

**ENRIQUE MORALES**  
Madrid, Spain



**Following the pathway from glomerular hyperfiltration to glomerulosclerosis**

**AVRY CHAGNAC**  
Tel Aviv, Israel



**ENRIQUE MORALES**  
Madrid, Spain

## Weight loss reduces proteinuria in obese CKD patients

*A potent, but little investigated and frequently overlooked therapeutic intervention*

Several epidemiologic investigations have confirmed that obesity is a significant risk factor for the appearance of proteinuria and end-stage kidney disease in a normal population. Obese patients present a much higher risk of developing hyperlipidemia, cardiovascular complications, hypertension, diabetes mellitus, and sleep apnea syndrome; however, there is scant information on the relationship between obesity and the risk of developing chronic kidney disease (CKD). In recent years, new publications have appeared that answer the question whether body mass index (BMI) is associated with the risk of developing CKD.

The relationship between obesity and proteinuria has been known to exist for more than two decades, when the first studies in which a minority of obese patients developed proteinuria were published. In the last decade, obesity-related nephropathy has become an increasingly frequent diagnosis, and recently published epidemiologic studies have unequivocally demonstrated a close relationship between BMI, the most precise parameter for quantifying the degree of obesity, and the risk of developing CKD in the normal population. In this regard, the beneficial effects for the kidney obtained by weight loss have become a key element in clinical and experimental studies. Obesity-related glomerulopathy may be explained by different pathogenic mechanisms, but its usual clinical presentation consists of a variable-range proteinuria without any noteworthy alterations in urine sediment. The appearance of proteinuria precedes the loss of GFR over the years.

In the last decade we have witnessed the development of numerous drug treatments for obesity. Recent studies have

demonstrated how the use of different drugs for weight reduction (sibutramine, rimonabant, orlistat), together with low-calorie diets, increase weight loss in obese patients with a suitable safety profile. Changes in lifestyle (regular physical exercise, absence of sedentary lifestyle) are other measures used to maintain weight loss. An important improvement in cardiovascular risk factors (dyslipidemia, insulin resistance) has been observed after weight loss in obese patients treated with pharmacotherapy and lifestyle modification. However, the influence on other parameters such as albuminuria, proteinuria, renal function or histologic lesions has not been investigated. Logically, weight reduction must be the most decisive therapeutic aspect; however, the evidence available for its influence is somewhat scant. In recent years there have been two interesting reviews (clinical trials and studies from the literature) that analyze in depth the effect of weight loss and its influence on proteinuria and renal function. Some studies have highlighted the relationship between reductions in proteinuria and/or albuminuria in obese patients who have been on a low-calorie diet.

The number of patients undergoing weight reduction surgery (bariatric surgery) has increased in recent years. To date, these operations are the most efficacious for losing weight in a population with morbid obesity. The beneficial effect of bariatric surgery is independent of the type of surgery performed, observing the same benefits with gastric bypass or gastric bands. Despite this evidence, no prospective studies have been conducted to investigate the possible beneficial effect of bariatric surgery in obese subjects with chronic kidney disease (CKD), and only some retrospective series with small numbers of patients and short follow-up have been reported. For this reason, we have designed a prospective, single-center, longitudinal and analytical study on the effect of weight loss in obese patients with CKD undergoing bariatric surgery. The aim of this study is to analyze the effect of bariatric surgery in obese patients (BMI >35-40 kg/m<sup>2</sup>) with CKD stages 1-3 (GFR >30ml/min/1.73m<sup>2</sup> and/or proteinuria >0.5 or

1g/24h), on parameters of renal damage (glomerular filtration rate, albuminuria/proteinuria), clinical and metabolic parameters (blood pressure, weight, cardiometabolic risk factors, glycemic control, insulin resistance, lipids), adipocyte inflammatory cytokines and markers of oxidative stress. Findings of the study will provide relevant and new information about the therapeutic role of bariatric surgery in obese patients with CKD.

There are multiple mechanisms through which the weight loss achieved by diet, physical exercise or drugs might reduce proteinuria: better blood pressure control, improved lipid profile (increase in HDL-cholesterol, reduction in LDL-cholesterol, reduction in triglycerides), improved insulin sensitivity, better glucose control in diabetic patients, a reduction in the concentration of leptin, reduction of glomerular hyperfiltration, a fall in activated components of the renin-angiotensin-aldosterone system (RAAS) and a reduction in inflammatory and oxidative stress processes. Naturally, the reduction in proteinuria that occurs after weight loss may be partly explained by the sum of these favorable changes. However, in the few clinical studies that have investigated the influence of these pathogenic mechanisms, the reduction in proteinuria is independent of blood pressure figures or lipid profile changes.

In conclusion, weight loss induces an important reduction in proteinuria in obese patients. It is important to point out that the antiproteinuric effect of weight loss is observed not only in obese and type 2 diabetic patients and in obesity-related glomerulopathy, but also in obese patients presenting with kidney diseases whose pathogenesis is not related to hyperfiltration. The reduction in proteinuria is rapidly observed and presents a significant correlation with the percentage of weight reduction. All this evidence clearly suggests that weight loss is a potent but little investigated and frequently overlooked antiproteinuric therapeutic measure, which furthermore provides a general improvement in the patient's metabolic profile. ■

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**AVRY CHAGNAC**  
Tel Aviv, Israel

# Following the pathway from glomerular hyperfiltration to glomerulosclerosis

*The role of glomerular hyperfiltration in renal disease in obesity and diabetes*

Glomerular hyperfiltration plays a major role in the pathogenesis of renal disease in obesity and diabetes mellitus, leading, in conjunction with other factors, to glomerulosclerosis.

## Effects of obesity and diabetes on renal plasma flow, glomerular filtration rate (GFR) and filtration fraction

The majority of investigations of renal hemodynamics in obese subjects with preserved renal function have shown increased glomerular filtration rate (GFR) and renal plasma flow, uncorrected for body size. GFR increased more than RPF in most studies, resulting in increased filtration fraction in the obese groups, with large interindividual variability. These changes were shown to appear at an early stage of adiposity, when body mass index (BMI) is below 30 kg/m<sup>2</sup>. Human data suggest that glomerular hyperfiltration is caused by an increased transmission of systemic arterial pressure to the glomerular capillaries through a dilated afferent arteriole, resulting in an augmented glomerular transcapillary hydraulic pressure difference<sup>1</sup>. Thus, systemic hypertension, being highly prevalent in overweight and obese people, also contributes to the pathogenesis of hyperfiltration-mediated renal disease. Renal hemodynamic studies performed in severely obese persons before and 1 year after bariatric surgery showed that following a decrease in BMI from 48 to 32, GFR, RPF and filtration fraction fell by 24%, 13% and 11%, respectively<sup>2</sup>. This investigation demonstrated that obesity-related glomerular hyperfiltration is reversible following weight loss, and established the cause-and-effect relationship between obesity and glomerular hyperfiltration. Similarly, glomerular hyperfiltration is also observed in types 1 and 2 diabetes, although less consistently. It should be noted that hyperfiltration may occur at the single nephron level when GFR is decreased.

Should GFR be indexed for body surface area (BSA)? The presence of glomerular hyperfiltration is often obscured by indexation of GFR to BSA. Since obese persons have an increased BSA, indexation results in normal GFR values, reflecting renal adaptation to metabolic needs. However, since the number of nephrons does not increase with increasing body fat, a rising GFR implies an increase in single-nephron GFR. Non-indexed GFR reflects this phenomenon, whereas correcting GFR for BSA obscures it. It should be noted that most equations used to estimate GFR provide BSA-indexed values.

## Effects of obesity on tubular reabsorption

The filtered sodium load in the obese and diabetic patient is increased in proportion to the degree of hyperfiltration. Thus, an increased reabsorption of salt along the nephron is indispensable to prevent volume depletion; however, in these 2 conditions, salt is reabsorbed in excess. Human studies showed that diabetic and obese non-diabetic subjects have increased fractional proximal reabsorption of sodium, decreased salt delivery to the macula densa leading to deactivation of the tubuloglomerular feedback and increased GFR. In diabetic subjects, the increased glucose filtered load results in an increase in proximal tubular glucose delivery and increased glucose reabsorption with sodium via the sodium-glucose co-transporter 2 (SGLT2). Experimental studies showed that obesity is also associated with activation of sodium transporters along the proximal tubule.

## Glomerular hyperfiltration: Primary renal vasodilation vs primary proximal tubular salt reabsorption

Two concepts compete to explain the obesity related glomerular abnormalities. The first proposed mechanism is the primary hemodynamic hypothesis, in which the primary event is vasodilation of the afferent arteriole. The second proposed mechanism is the tubulocentric hypothesis, in which the primary event is increased proximal reabsorption of salt and water, resulting in decreased solute delivery to the macula densa, deactivation of the tubuloglomerular feedback, preglomerular vasodilation and consequent glomerular hyperfiltration. Non-diabetic obese as well as diabetic people have increased fractional proximal sodium reabsorption. Acetazolamide, a carboanhydrase inhibitor reducing proximal sodium reabsorption, decreases GFR<sup>3</sup>. A similar reduction in GFR follows SGLT2 inhibition. Both interventions increase solute delivery to the macula densa, activate tubuloglomerular feedback and thus decrease GFR. These effects are compatible with the tubulocentric theory, but do not prove or disprove either concept.

## Factors leading to glomerular hyperfiltration and abnormal salt handling: Hormonal and neurohormonal activation

The renin angiotensin aldosterone system (RAAS) and the renal sympathetic nervous system (RSNS) are over-activated in obesity and in diabetes. Levels of RAAS components are increased, both in the circulation and in renal tissue. RAAS over-activation may be involved in the pathogenesis of hyperfiltration in different ways:

1. A direct glomerular effect: A-II and aldosterone vasoconstrict glomerular arterioles, the efferent more so than the afferent arterioles. This effect is expected to decrease GFR;
2. Excessive sodium reabsorption causing hypertension and hyperfiltration: A-II increases sodium reabsorption directly in the proximal and distal nephron and indirectly through activation of mineralocorticoid receptors.

Over-activation of the RSNS may also induce sodium retention in diabetic and in obese patients. Obstructive sleep apnea is one of the factors activating the renal sympathetic system in obesity. Sodium retention induced by activation of the RAAS and RSNS leads to hypertension and increased glomerular pressure, resulting in increased single-nephron GFR.

## Consequences of Glomerular Hyperfiltration and Abnormal Salt Handling

### Physiologic consequences:

The prevalence of albuminuria is increased in obese and diabetic people. Both hemodynamic and non-hemodynamic factors contribute to this increased albumin excretion.

Obesity-associated hyperfiltration is usually associated with increased filtration fraction. This results in hemoconcentration and increased oncotic pressure in peritubular capillaries that promotes proximal tubular sodium reabsorption. Thus, glomerular hyperfiltration itself may enhance sodium reabsorption by raising peritubular oncotic pressures.

### Structural consequences:

The increased hydrostatic pressure in the glomerular capillaries drives an increased circumferential and axial capillary wall stress, which induces basement membrane expansion and glomerulomegaly, and an increased ultrafiltrate flow

entering Bowman's space. The latter exerts a high fluid shear stress on podocytes, prompting podocyte maladaptive hypertrophy, which finally leads to podocyte detachment and ultimately - to glomerulosclerosis. The fluid shear stress exerted on podocytes activates various mediators that may be involved in podocyte hypertrophy, apoptosis, decreased adhesion and detachment. This mechano-transduction may also release pro-fibrotic mediators.

A human biopsy study in hyperfiltrating non-diabetic obese patients revealed dilated Bowman's space and proximal tubular lumen, most probably as a consequence of the glomerular hyperfiltration. Thus the dilated glomerular and tubular urinary space may represent a morphologic sign of glomerular hyperfiltration.

In conclusion, glomerular hyperfiltration and glomerular hypertension play a role in the pathogenesis of kidney disease in diabetic and obese subjects by causing podocyte damage through mechano-transduction and maladaptive glomerular hypertrophy, leading to glomerulosclerosis. Thus, reducing glomerular hyperfiltration may effect a slower rate of progression of obesity-related and diabetic kidney disease. ■

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# Protecting heart, vessels and bone – new ways to control phosphorus and potassium



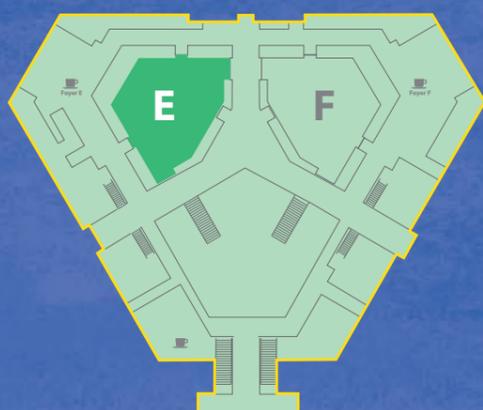
Chair: Professor Markus Ketteler  
Co-Chair: Professor Alexander Rosenkranz

**Sunday 22 May 2016**

**13:30–15:00**

Hall E, Level 0

Austria Center Vienna



## Programme

**13:30** Lunch boxes will be provided

**13:45–13:50** Chairs' introduction

Marcus Ketteler (*Coburg, Germany*)

Alexander Rosenkranz (*Graz, Austria*)

**13:50–14:10** Hyperphosphataemia – understanding the challenges

Laurent Juillard (*Lyon, France*)

**14:10–14:30** Advances in the management of hyperphosphataemia

Philip Kalra (*Manchester, UK*)

**14:30–14:50** A new approach in potassium management – can we change the treatment paradigm?

Matthew R. Weir (*Maryland, USA*)

**14:50–15:00** Closing remarks and Q&A

Marcus Ketteler, Alexander Rosenkranz

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## European Renal Nutrition (ERN) – an official Working Group of the ERA-EDTA



Current chairman of the working group is **Denis Fouque, France**

Find more information at [www.era-edtaworkinggroups.org/en-US/group/european-renal-nutrition](http://www.era-edtaworkinggroups.org/en-US/group/european-renal-nutrition)

The aim of the European Renal Nutrition Working Group is to conduct research on the impacts of lifestyle, diet, nutrient homeostasis and protein-energy wasting (PEW) management on chronic kidney disease (CKD) outcomes. European research in this field is already of high quality, but hampered by reduced funding, small

patient cohorts and scientific isolation. ERN aims to forge strong collaborative links at a multinational European level in order to deepen our understanding of nutrition and CKD complications. Apart from initiating scientific projects, the Working Group organizes regular CME courses.



**VINCENZO BELLIZZI**  
Salerno, Italy

## It's time to emphasize quality of life in older dialysis patients

*A patient-focused approach adds health to years, not just years to life*

The global population is aging rapidly. In response, the World Health Organization (WHO) has launched an innovative project on aging and health to "ensure that older people in all countries can experience both long and healthy life" [1]. A healthy life is a life with a preserved ability to function in old age rather than a life in the absence of disease. Hence, according to WHO, "healthy aging is the process of developing and maintaining the functional ability that enables well-being in older age". The task now is to move from the prevalent aim of adding years to life toward the wish to add "health" to years through a holistic approach that addresses health problems and functional capacity to provide a good quality of life in older people. The WHO Guidelines, Integrated care for older people (ICOPE) should be available in May 2016.

In elderly patients with advanced renal disease, the start of dialysis has a dramatic impact on their functional status

[2]. The degree of independence in several activities of daily living (eating, dressing, toileting, walking, standing, changing position in the bed, ...) declines by more than 30% after 3 months of dialysis. At this time, 39% of patients maintain their functional capacity, but at 12 months only 13% maintain their predialysis functional status. On the whole, the frequency of maintenance of functional status is very low after the start of dialysis. The trajectory of functional capacity decline in renal disease patients starts around three months before dialysis inception, stabilizes in the subsequent one to four months and then continues to decline. Hence dialysis, while improving uremia and possibly prolonging the life of the older patient with advanced chronic kidney disease (CKD), cannot restore healthy functional status that is preserved in only one out of eight patients. Functional impairment after initiation of dialysis is more pronounced in the oldest and hospitalized patients. The magnitude of functional decline is, however, independent of age, gender, race and also of its trajectory prior to dialysis. The reason why functional capacity declines in dialysis is not clear and whether dialysis per se has a causative role also remains ill defined.

Generic health-related quality of life (HRQOL) in dialysis patients is reduced compared to the normal population all over

the world. Some differences among subscales of HRQOL in dialysis emerge in different continents: US patients have highest scores for mental health domains, while Japanese patients have better physical functioning but also a greater burden of kidney disease. In older people, HRQOL is similar among hemo- or peritoneal dialysis patients, but residual renal function seems to be associated with a better HRQOL in hemodialysis.

Specifically, ESRD affects physical functioning, and these domains are strictly related to common nutritional markers (albumin, creatinine, body mass index [BMI], energy intake). In contrast, traditional basic dialysis indicators (PTH / calcium / phosphate, dialysis dose, inflammation) are not related to these domains. Interestingly, low HRQOL is associated not only with low serum albumin and creatinine, but also with higher body fat (a surrogate marker of nutritional reserve). This observation is puzzling since body fat, while being protective (survival advantage of high BMI in dialysis or obesity paradox), is also associated with a perceived lower quality of life that is related to worse outcomes. Nutritional markers in dialysis are linked to HRQOL even among well-nourished patients. Hence, nutrition may have a central role in the HRQOL in dialysis patients. This assump-

## A more active lifestyle for older dialysis patients

*Implement exercise programs*

Most dialysis patients are sedentary, especially older dialysis patients. This fact is confirmed by many studies that evaluate physical activity using questionnaires or pedometers. This inactivity is associated with increased mortality; in contrast, the benefits of physical activity in terms of morbidity and mortality are numerous in this population.

Recommendations exist for older dialysis patients: those set out for the general elderly adult population. However, few centers are implementing exercise training programs in dialysis patients. There are many reasons, including lack of knowledge and time of the medical staff, and the incorrect belief that older dialysis patients are not able or would refuse to increase their physical activity.

Initial assessment is essential, using simple means such as measurement of gait speed or the Timed Up and Go test,

and medical examination. Different types of exercise can be proposed, adapted to the physical capacity of the patients. Ideally, aerobic exercise and resistance exercise should be combined, and be suggested, even if their intensity is very low because of the patient's physical and functional limitations. It is important to note that no serious adverse events have been reported in the different programs and their feasibility has been demonstrated even in older dialysis patients.

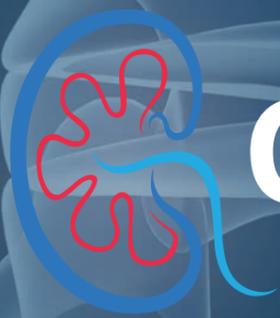
Cycling during each dialysis session is an easy program to implement in the dialysis unit, with good adherence by the patient, using the time that contributes to deconditioning, and the presence of medical staff to provide the confidence and encouragement to continue. The intensity and duration of the exercise can be increased gradually. Resistance exercise using elastic bands can also be proposed during dial-



**ANNE KOLKO-LABADENS**  
Paris, France

ysis, as well as exercise on the days without dialysis with a coach or physiotherapist, alone or with other patients.

The fight against sedentary lifestyle among dialysis patients should be a goal of health care teams. There is no reason to regard age as a barrier; on the contrary, older patients could benefit from a physical activity program by an improvement of quality of life and physical functioning, leading to the preservation of their autonomy in daily activities. ■



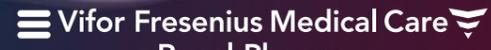
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tion supports further interest in intensive nutritional care in dialysis. Nutritional interventions could improve both nutrition and HRQOL in dialysis, but interventional data are very scarce. Evidence available to date suggests that nutritional supplementation during dialysis does not have any effect on short-term surrogates of HRQOL.

Large scale, worldwide, observational studies indicate that HRQOL is strongly related to dialysis patients' outcomes. Lower scores for mental and kidney disease domains, but mostly for the physical domains of HRQOL, are associated with higher risk of either hospitalization or death, irrespective of demographics and comorbidities. Elderly patients, however, deserve special consideration. Indeed, older patients with advanced kidney disease and multiple comorbidities, who decide not to start dialysis, have reduced survival but maintain their HRQOL. A critical question therefore arises: which wins the challenge in elderly dialysis patients: length or quality of life?

Across decades, the quality of life of patients on dialysis based on traditional indicators (anemia, dialysis dose, weight, PTH/phosphate, etc.) has remained mainly unchanged though manifesting some clinical improvements. A new quality model to improve the quality of life in dialysis people has been suggested [3]. The model incorporates the basic indicators into more complex, intermediate outcomes (fluid, diabetes, medication and mental status management, etc.). This approach would move from biochemical-centered to patient-centered care. For CKD patients, length of life is important but what matters most is improving the quality of their lives. Patients are willing to sacrifice life expectancy to reduce the hospital visits and other restrictions related to treatment and also to gain opportunities to travel or to have a more active live. Improving the intermediate outcomes by sharing the aim with the patient will improve the major outcomes (survival, hospitalization) and their overall quality of life. There is as yet no specific

or unique formula to accomplish such patient-focused care in advanced renal disease. Different types of care may be needed for different types of patients and also to meet their different preferences. ■

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## Session

**ERN/CME 6**

**As we grow old – nutritional considerations for the CKD elderly patient**

**TODAY, 09.00–12.15  
HALL K**

(continued from page 12) M2 macrophages and reduction of albuminuria and glomerular sclerosis. Therefore, strategies targeting inflammation can induce therapeutic effects on diabetic kidney disease by several mechanisms and one such mechanism could be preservation of M2 reparative macrophages in the damaged kidney. Ex vivo programmed M2 macrophages displaying an anti-inflammatory or reparative phenotype have been used with discordant results as a macrophage cell therapy in distinct injured kidney mouse models, including IRI, lupus nephritis and adriamycin nephropathy. We have explored this approach in several models of chronic nephropathy, including diabetic kidney disease. Infusion of bone marrow-derived M2 macrophages in the unilateral ureteral obstruction mouse model did not induce any therapeutic effect. In fact, these M2-infused macrophages became functional and phenotypically M1 when they entered the damaged kidney, probably in response to the high expression of renal proinflammatory molecules. Other authors showed that this limitation can be partially overcome by using macrophages with low proliferative capacity. We found similar results in diabetic kidney disease. Infusion of bone marrow-derived M2 macrophages in a db/db mouse model aggravated albuminuria and renal damage. In order to provide insight into macrophage polarization as the major limitation of macrophage cell therapy in chronic nephropathies, we decided to stabilize M2 macrophages by lipocalin-2 transfection before their infusion. Interestingly, M2-NGAL macrophage cell therapy was associated with reduction of albuminuria. This therapeutic effect was associated with preservation of macrophage M2 phenotype and function when M2-NGAL infused macrophages were isolated from the kidney.

In conclusion, macrophage plasticity is a major hurdle for the success of M2-macrophage cell therapy in chronic nephropathies that could be overcome by using M2-macrophages with a low proliferative ability or by ex-vivo macrophage stabilization strategies. ■

# ERA-EDTA European Dialysis Working Group (EUDIAL)



Current chairman of the working group is  
**Peter J. Blankestijn, The Netherlands**

Find more information at  
[www.era-edtaworkinggroups.org/en-US/group/eudial](http://www.era-edtaworkinggroups.org/en-US/group/eudial)

EUDIAL is dedicated to the development and evaluation of innovative renal replacement therapies. It has been decided to focus at first on convective renal replacement therapies. The rationale for that decision is supported by several facts, including increasing interest in

convective therapies, translating to rapid growth in the number of patients treated by modern versions of these therapies, and by several reports suggesting an improvement in CKD patient outcomes. Apart from initiating scientific projects, EUDIAL organizes regular CME courses.



**CARLO BASILE**  
Acquaviva delle Fonti, Italy

## Why choose high volume online post-dilution hemodiafiltration?

*Growing evidence that it is associated with improved survival*

The first fundamental question that needs to be addressed is: why do we need new dialysis treatment options? Because, despite improvements in technology and patient care, the mortality rate of patients on maintenance dialysis remains alarmingly high at approximately 15 to 20% per year.

A second basic question is: why do we need convective clearance? Because retention of middle-molecular weight uremic toxins has been related to mortality in patients with end-stage kidney disease. Therefore, interest has shifted from purely diffusive dialysis techniques, such as low-flux hemodialysis (HD), which remove mainly low-molecular weight solutes, towards convective therapies, such as hemodiafiltration (HDF), which also remove larger solutes. In the last few years, three large, prospective, randomized controlled trials (RCTs) have been conducted in different European countries to compare survival outcomes in prevalent patients receiving conventional HD and online post-dilution HDF (OL-HDF).

In the Convective Transport Study (CONTRAST), 714 prevalent HD patients were randomly assigned to undergo either OL-HDF (post-dilution, target convection volume 6 liters/h) or low-flux HD. The primary outcome was all-cause mortality. The main secondary endpoint was a composite of fatal and non-fatal major cardiovascular events. After a mean follow-up of 3.0 years, the incidence of all-cause mortality was not affected by treatment assignment. However, subgroup analysis suggests benefit on all-cause mortality (hazard ratio 0.57;  $p < 0.016$ ) among patients treated with high convection volumes ( $> 20$  liters/treatment).

The Turkish OL-HDF Study compared the effects on morbidity and mortality outcomes for OL-HDF and high-flux HD. Seven hundred and eighty-two patients were randomly assigned at a 1:1 ratio to either OL-HDF or high-flux HD. The follow-up period was 2 years. The primary outcome was the composite of death from any cause and non-fatal cardiovascular events. There was no statistically significant difference between the two treatments. However, in a post-hoc analysis OL-HDF with substitution volume  $> 17.4$  liters was associated with a 46% reduction ratio for overall mortality ( $p = 0.02$ ) and a 71% reduction ratio for cardiovascular mortality ( $p = 0.003$ ).

Finally, in Catalonia (Spain), the ESHOL trial assigned 906 patients either to continue HD or to switch to high-efficien-

cy OL-HDF. ESHOL is the first randomized study to show a significant advantage for OL-HDF, reducing all-cause mortality by 30% (primary outcome,  $p = 0.01$ ), cardiovascular mortality by 33% (secondary outcome,  $p = 0.06$ ) and infection-related mortality by 55% (secondary outcome,  $p = 0.03$ ). Mean convective volumes were 23.7 liters per session; mean blood flow rate 387 ml/min and mean dialysis time 236 min.

These three RCTs contain several potential risks of bias, leading to either an over- or underestimation of the true effect. An individual participant data meta-analytic approach might solve several methodological problems and increase the level of evidence for a potential effect of HDF on morbidity and mortality. In fact, this analysis was performed using data from CONTRAST, Turkish OL-HDF Study, ESHOL and a fourth not-yet-published French HDF study. It showed that online HDF reduced the risk of all-cause mortality by 14% and cardiovascular mortality by 23%. There was no evidence for a differential effect in subgroups. The largest survival benefit was for patients receiving the highest delivered convection volume ( $> 23$  liters per 1.73 m<sup>2</sup> body surface area per session), with a multivariable-adjusted hazard ratio of 0.78 for all-cause mortality and 0.69 for cardiovascular disease mortality [1].

Finally, four large meta-analyses on convective therapies have been published in the last two years, which, however, showed a discordant outcome. It appears that these analyses differ in the number of studies and patients included, the definitions of comparator and intervention therapy and

types of studies, which varied from small observational to large prospective RCTs. As far as the intervention arm is concerned, in our opinion, a statement on today's convective therapies should be based on a convection volume of at least 17–19 liters/session in the post-dilution mode. The only meta-analysis that largely fulfils this criterion shows that HDF was associated with a decreased risk of mortality of 16% and of cardiovascular mortality of 27% [2]. Taken together, the above studies lead to the conclusion that high volume post-dilution OL-HDF is associated with improved overall survival. This advantage results entirely from a lower cardiovascular mortality.

Now, the third and crucial question is: why should it be so? What are the underlying mechanisms? Are the aforementioned RCTs confounded by the favorable profile of HDF patients at entry to the study? Although this cannot be completely ruled out, it should be mentioned that extensive corrections were made in all RCTs. In theory, both a decrease in the incidence of heart failure, ischemic heart disease, sudden cardiac death and stroke may play a role. Interestingly, in ESHOL a reduction in stroke was found, while the incidence of heart failure and ischemic heart disease was similar. None of the three recent RCTs found a difference in sudden cardiac death between HD and HDF. Echocardiographic studies reported in the literature indicate that the functional and structural deterioration of the left ventricle over time in HD patients is mitigated or even absent in HDF. Thus, the advantage of high volume post-dilution OL-HDF could be possibly due to better preservation of left ventricle mass and function.

	Prescription	Recommendations
Vascular access	Arteriovenous fistula or graft Central venous catheter	First option Increase session duration
Access blood flow rate (Q <sub>b</sub> )	350 – 500 ml/min	The maximum possible
Dialysate flow rate	400 – 500 ml/min + infusion flow rate	No influence on convective dose
Infusion flow rate	25 – 33% of Q <sub>b</sub> , 90 – 160 ml/min	The maximum possible
Session duration	4.0 – 5.0 h/session	The maximum possible
Convective volume (replacement volume + intradialytic weight loss)	$> 23$ litres/session	The maximum possible
Percent convective volume of the blood volume processed	25 – 30%	The maximum possible
Dialyzer	High flux membrane	Avoid membranes with high adsorption capacity

**Table 1: Recommendations to obtain the optimal high volume online post-dilution HDF dose** © Basile

May improved stability of intra-dialytic blood pressure contribute to the beneficial effect of high volume OL-HDF on survival? Intra-dialytic hypotension (IHD) is a common problem in HD, and has been related to cardiac stunning, bowel ischemia and brain hypoperfusion. Observational studies now suggest that IDH is strongly associated with poor outcomes, and especially poor cardiovascular outcomes. The occurrence of IHD was not mentioned in the primary CONTRAST paper; IDH was a secondary outcome in the Turkish OL-HDF Study, but results were not described in the primary paper. In the ESHOL trial IDH was monitored and the results were reported: in the HDF group, there were 679 episodes of IDH per 100 patient-years vs. 938 episodes of IDH with HD, a difference that was highly statistically significant.

Treatment with cooled dialysate reduces IDH, HD-induced brain injury and improves cardiovascular survival. Two large RCTs reported that blood pressure stability during HDF was superior to HD. However, when cool dialysate was used both in HDF and HD, blood pressure, blood volume, cardiac output and microcirculation did not differ. Unfortunately, none of the three recent RCTs in high volume OL-HDF reported dialysate temperature. Temperature balance studies would suggest that, if the cause of slight extracorporeal cooling with post-dilution HDF is due to the slightly lower temperature of the substitution fluid stream then, all other things

being equal, increasing the substitution fluid infusion flow rate should result in more extracorporeal circuit cooling.

There is no compelling evidence that high volume post-dilution OL-HDF reduces mortality by improvements in traditional (such as high blood pressure and cholesterol levels) and non-traditional risk factors (such as toxicity of uremia itself and the bio-incompatibility of the extra-corporeal system). With respect to solute removal, neither  $Kt/V_{urea}$  nor  $\beta_2$  microglobulin were related to survival. None of the meta-analyses or RCTs reported a decline in other causes of death, such as withdrawal from dialysis or malignancies. Infectious complications, which account for one quarter of total mortality in end-stage kidney disease, are usually linked to bacterial spread from vascular access, particularly in the case of central venous catheters. Whereas no overall difference was found in CONTRAST, infection-related mortality in ESHOL was lowest in HDF patients. Whether this outcome results from a lower central venous catheter use in the HDF group (7% in the HDF group vs. HD 13%) or from the high convection volumes applied remains to be established.

#### Take home messages

- Recommendations to obtain the optimal high volume post-dilution OL-HDF dose are reported in Table 1.

- High volume post-dilution OL-HDF is associated with improved overall survival. This advantage results entirely from a lower cardiovascular mortality, possibly due to better preservation of left ventricle mass and function.
- Improved intra-dialytic blood pressure stability may contribute to the beneficial effect of high volume post-dilution OL-HDF on survival.
- The beneficial effect of high volume post-dilution OL-HDF on survival is not restricted to selected subgroups, such as age, comorbidity or dialysis vintage.
- There is no compelling evidence that high volume post-dilution OL-HDF reduces mortality by improvements in traditional and non-traditional risk factors. ■

## Exploring the clinical benefit of online hemodiafiltration

*The evidence is accumulating, but questions remain to answered*



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Convective renal replacement therapies, especially online hemodiafiltration, are attracting increasing scientific and clinical interest. The number of patients treated with online hemodiafiltration is growing, and the highest prevalence of end-stage kidney disease (ESKD) patients treated with this modality is found in Europe. The European nephrology community has been leading in this field of renal replacement therapy for more than two decades.

Randomized controlled trials comparing the outcomes of ESKD patients treated either with online hemodiafiltration or with conventional hemodialysis have been concluded over the past few years. A recent meta-analysis of all individual data of these available trials, which was done with the financial help of EuDial, suggests improved clinical outcome in patients who are on online hemodiafiltration. This is especially the case when convection volume is  $\geq 23$  L / session (which equates to approximately 70 L / week) [1,2]. The need for this 'minimum dosage' to fully obtain the benefits of online hemodiafiltration has been confirmed by large observational studies.

The convection volume actually achieved per treatment session may differ from the set target volume. Main determinants of achieved volume are treatment time (4h / session or more), blood flow rate through the extracorporeal circuit (minimum of 350-400 ml / min) and set filtration fraction (ratio of ultrafiltration volume / blood flow rate through the ex-

tracorporeal circuit: aim at 30 – 33%). Studies suggest that when these factors are taken into account, the minimum convection volume of 23 L / session can be achieved in the great majority of patients [3].

So far, the mechanism(s) of this beneficial effect is(are) not completely understood. These may include: improved hemodynamic stability, enhanced clearance of uremic toxins, reduced chronic inflammatory state, and others. Importantly, none of the trials have raised any safety concern about the large-scale use of online hemodiafiltration.

In this presentation, the available clinical evidence on online hemodiafiltration as compared to standard hemodialysis will be discussed. Further, safety issues potential barriers to start and implement online hemodiafiltration and possible mechanism(s) of a beneficial effect will be discussed [4, 5].

Still questions remain open. So, for the near future the EuDial Working Group will remain focused on increasing the knowledge in this field, and also on organizing CMEs and other activities to review and share the information with others. Future studies should focus on the mechanism(s) of a beneficial effect of online hemodiafiltration. Further, little is known about its effects on aspects of quality of life. Any clear improvement may be very relevant, especially in the absence an effect on so-called hard clinical endpoints. Most studies so far have used in the currently more-or-less accepted standard schedule of three treatment sessions per week. Virtually no data exist on the role of online hemodiafiltration in more intensive schedules such as daily and nocturnal dialysis. Finally, only a few studies have evaluated the role of online hemodiafiltration in paediatric nephrology, where the treatment may have advantages as compared to standard hemodialysis. ■

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**Hemodiafiltration: acceptance and regulatory issues worldwide**

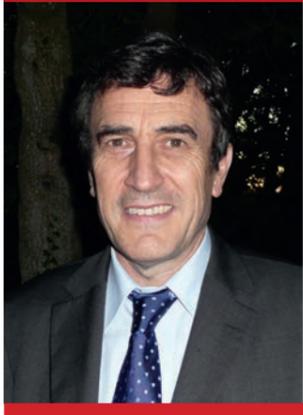
**BERNARD CANAUD**  
Montpellier, France

## Session

**EUDIAL / CME 4**

**Hemodiafiltration – the new standard of care?**

**TODAY, 09.00 – 12.15  
HALL C**



**BERNARD CANAUD**  
Chief Medical Officer of Centre  
of Excellence Medical  
FMC EMEA  
Bad Homburg, Germany, and  
Montpellier, France

Co-author: Katrin Koehler

# Hemodiafiltration: acceptance and regulatory issues worldwide

*Hemodiafiltration is now at the crossroads of a new paradigm shift*

Progress in end-stage kidney disease (ESKD) patient management over the past years has been marked by several paradigm shifts in renal replacement therapy (RRT) with dialysis. These changes in ESKD care have been dictated by unmet medical needs, side effects of conventional hemodialysis (HD), changes in patient medical profile (aging, comorbidities), logistic and / or cost constraints, as well as advances in the understanding of uremic pathophysiology. In brief, hemodialysis has moved from long to short dialysis, from acetate to bicarbonate, from bioincompatible to biocompatible, from low flux to high flux, from uncontrolled to controlled ultrafiltration, from contaminated to ultrapure dialysis fluid, and finally from purely diffusive (small uremic toxins) to enhanced convective (middle and large uremic toxins) modalities.

## Paradigm shifts in RRT

In line with these paradigm shifts, online hemodiafiltration (HDF) has come of age to represent today the most advanced and innovative form of RRT. By combining high diffusive and enhanced convective clearances, HDF offers the most efficient form of dialysis over a wide spectrum of uremic toxins; by using ultrapure dialysis fluid and high-flux synthetic dialysis membranes, HDF provides the most biocompatible method; and by using dedicated smart HDF systems it has become as simple to use as conventional dialysis. Over the last decade, accumulating clinical evidence has confirmed the safety, reliability and sustainability of the online method, but has also proved the superiority of HDF over conventional hemodialysis on clinical endpoints and patient outcomes, both in cohort studies and in randomized controlled trials provided the right convective dose was delivered.

In this context, it is not surprising to observe a significant and rapid increase in the acceptance rate of HDF by the nephrology community in order to reduce intradialytic morbidity, improve long-term chronic disease patient outcomes and reduce the overall burden of disease. Thus, in this brief article we aim, firstly, to report on current use and epidemiologic trends of HDF worldwide as well as on practice patterns in HDF prescription; secondly, to analyze factors that may affect HDF clinical acceptance and more widely its implementation; and thirdly, to elaborate on remaining aspects that need to be explored and elucidated for further development and optimal use of HDF. The overview and analysis is based on consolidated data from Fresenius Medical Care's Market Survey, national database registries, scientific society reports as well as databases of recent studies, and has been complemented by research and communication in the field.

## Prevalent use and epidemiologic trends of HDF worldwide

In 2014, 2,662,000 ESKD patients were on RRT with dialysis worldwide. There were 2,358,000 patients (89%) on hemodialysis and 304,000 patients (11%) on peritoneal dialysis. Among hemodialysis patients were 163,000 patients on hemodiafiltration, representing a share of 7%. The online method was the most prevalent HDF modality, accounting for 152,000 patients (94%) while the conventional or 'bag' HDF modality was much less well represented, accounting for 10,500 patients (6%).

It is interesting to note that the utilization of HDF differs significantly worldwide. Large variation exists in the distribution of HDF across the four main regions of the globe, briefly defined as Europe, Middle East and Africa (EMEA), Latin Amer-

ica (LA), Asia Pacific (AP) and North America (NA). EMEA and AP regions account for the vast majority of HDF-treated patients with 97,900 (16%) and 63,200 patients (6%) respectively, while LA and NA regions account for 1,120 (<1%) and 630 patients (<1%) respectively. With its share of 16%, Europe is considered the most relevant HDF region in the world, also accounting for over 60% of the global HDF population. Regarding the absolute numbers of HDF-treated patients in the EMEA region, ten countries account for 69,620 HDF-treated patients, representing a share of 43% of total HDF-treated population. Germany, Italy, France, United Kingdom, Portugal and Spain are the countries with the largest HDF patient population. As their counterparts in the AP region, Japan and China (including Taiwan Province of China) are the most prominent countries in terms of HDF share, accounting for 34,500 and 18,100 patients respectively with a share of 21% and 11%. In contrast, the Middle East and Africa (MEA), LA and NA, with a share of 3%, cover only a small number of HDF-treated patients (4,930).

Over the period from 2006 to 2014 the absolute number of HDF-treated patients worldwide has grown from 50,300 to 163,000 patients, representing a 16% compound annual growth rate, while in the meantime HD patient growth rate was only 7.2%. Interestingly, regarding the two main regions delivering HDF (Europe and AP), the patient compound annual growth rate was 16.5% and 14.5% respectively, while the average patient growth rate for RRT with dialysis was 4.4% in Europe and 10.5% in AP.

## Key factors affecting HDF clinical acceptance worldwide

While it remains unclear which factors most influence the development and the use of HDF, it is intuitively easy to postulate that three groups of factors may have a direct impact on HDF acceptance: firstly, regulatory and technical issues; secondly, patient benefits and clinical evidence; thirdly, healthcare policy and reimbursement rates. Europe and Japan, caring for more than 75% of HDF-treated patients worldwide, will in the following paragraphs be used to illustrate these issues.

In Europe the prevalent use of HDF varies tremendously across countries. On average, the HDF share is 15% as part of the total dialysis population but it varies from almost zero up to 84% in Switzerland. Notably, Europe may be clustered in four regions, three being close in terms of their HDF-prevalent use including Northern, Central, and Western Europe with more than 25% respectively, while Eastern Europe's share is only around 14%. In the latter case, the lower share is less attributable to technical or regulatory aspects since all material is CE marked, or to the lack of clinical evidence since most of the studies were developed in Europe. It rather reflects that respective healthcare policy making and reimbursement rates might be limiting the access to HDF therapy.

In Japan the prevalent use of HDF is 14.5% of the total dialysis population (298,924 patients in 2014). Importantly, healthcare authorities and policy makers revised the conditions of HDF practice in 2010 and 2011 by certifying online methods and recognizing HDF as premium therapy. As a result, the HDF share, which was flattening around 5% until 2011, started to increase with patient average annual growth rate achieving 41% in 2014. In that case, the flattening use of HDF observed before 2011 was deliberately bridled and curbed by regulatory authorities and policy makers, rather than by clinicians or technical aspects.

Based on the present trend and progression it could be roughly estimated that the number of patients treated by HDF might reach the 500,000 mark over the next five years.

## Further development and fine-tuning of HDF prescription

It has become evident over the past years that beneficial effects of HDF are dose-related to the total ultrafiltered volume per session and cumulated over the week. In addition, it is also clear that the convective dose needs to be customized to patients' metabolic characteristics and should fit with global dialysis adequacy targets. Yet, whether this convective dose needs to be scaled to patient characteristics, such as body weight, body mass index (BMI), body surface area (BSA) or total body water, remains a matter of debate.

In line with this crucial and sensitive determinant of HDF efficacy, all efforts should be undertaken by caregivers to probe and achieve the optimal convective dose in order to enable full benefits of the therapy. Practice patterns of HDF differ significantly worldwide and need to be aligned to provide a sound basis for clinical comparison.

Among prescription patterns the three following elements are of particular note: firstly, the substitution modality, which affects HDF solutes clearances; secondly, the optimal convective volume for patient benefits, which could vary from region to region due to ethnicity and anthropometric features; thirdly, the total treatment time duration, which affects solute mass removal and hemodynamic tolerance. As far as the substitution modality is concerned, tremendous differences are noticeable between Europe and AP region. Briefly, in Europe 90% of HDF-treated patients are on post-dilution mode receiving 21 liters per session on average, on the basis of a four hours three-times-weekly treatment with a mean blood flow of 350 ml / min, while in Japan 90% of HDF patients are on a pre-dilution mode receiving 40 liters per session on average, on the basis of a five hours three-times-weekly treatment with a mean blood flow of 180 ml / min. The dilution factor that affects these substitution modalities should be accounted for in order to achieve the same convective dose and comparable solute mass removal. Furthermore, regarding the recent trend to move to higher convective volumes targeting improved patient outcomes, it is important to consider its impact on electrolyte mass balance (e.g. sodium, potassium, calcium, magnesium, chloride, bicarbonate) and also on potential increase of unwanted solute mass removal (e.g. amino acids, small peptides, nutrients, albumin loss).

## Hemodiafiltration as a new standard of care in RRT

Today, online HDF represents a new paradigm shift in RRT with promising clinical results. The related dialysis dose concept should integrate both components of mass solute removal, i.e. diffusive and convective dose.

HDF acceptance is growing fast in the two leading regions that have approved the method – i.e. Europe and Asia Pacific – with a patient average growth rate of 15.8%, being far above the total patient RRT growth rate in these regions of 4.4% and 10.5% respectively. Interestingly, some initiatives have recently been launched to facilitate the implementation of HDF in the Americas. These could even provide the definitive push for promoting HDF as a new standard of care in ESKD patients worldwide. ■

## EURECA-m Working Group – an official Working Group of the ERA-EDTA



The aim and scope of EURECA-m (EUropean RENal and CARdiovascular Medicine) is to foster collaboration in the overlap between cardiovascular and renal medicine. Collaborative links between investigators from different specialties and effective bridging of interspecialty knowledge are complex affairs which pose a range of challenges, from differences in the

perception of priorities to difficulties in setting common goals. EURECA-m will make special endeavors to help create a common nexus for nephrologists, cardiologists, hypertensionologists and diabetologists. In addition to initiating joint scientific projects and partnerships, the EURECA-m also organizes regular CME courses.

Current chairman of the working group is

**Gérard Michel London, France**

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**RAYMOND  
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## Future advances in decreasing uremic toxin concentration

Considering the current status of extracorporeal strategies, major advances have been made to improve uremic toxin removal, but dialysis adequacy with current options may almost have reached its maximum capacity. Taking into account the beneficial dose response that is obtained in many biological studies on uremic toxins, there is room for a further decrease in their concentration, but a shift of paradigm may be necessary to reach that target. In this presentation, we will consider the options.

The uraemic solutes for which the drive to enhance their removal is most prominent are the protein-bound retention solutes and the larger 'middle molecules'. Indeed, there is ample experimental evidence that protein-bound solutes interfere with a host of damaging biological processes. At the clinical level, their relation to hard outcomes has essentially been shown in observational studies, whereas randomized controlled trials are missing. This can be attributed, at least in part, to a lack of therapies that specifically remove those molecules. With middle molecules, the available information is the other way around. Here, experimental evidence is not so convincing, but randomized controlled trials applying large-pore high flux membranes, known for removing especially larger molecules, have shown outcome advantages.

The current state of the art with regard to dialysis strategies points to large-pore membranes being advantageous for removal of the middle molecules, which is further enhanced by adding convection to diffusion, as in hemodiafiltration. The latter may also be slightly superior to other strategies for the removal of protein-bound toxins. However, the impact on day-to-day serum concentration of protein-bound toxins may be not too impressive. Remarkably, in spite of a markedly lower clearance capacity for protein-bound solutes with peritoneal dialysis (PD) compared to high-flux haemodialysis, their serum concentration is lower with PD. These data suggest that mechanisms other than dialysis, essentially metabolic factors, may impact uraemic toxin concentration under certain conditions.

Are there ways to further optimize extracorporeal removal with hemodialysis and related strategies? Increasing blood or dialysate flows might be a basic option, but removal curves

tend to level off in the higher flow ranges. In addition, each increase in efficacy is partly offset by a rebound phenomenon that gains in importance as removal becomes more prominent. The only gain in efficacy that does not result in an increasing rebound is by prolonging dialysis. This allows larger shifts of difficult-to-remove solutes from the extra-plasmatic to the plasmatic compartments, thus facilitating removal of those solutes into dialysate. Extending dialysis duration is therefore a most efficient way to improve elimination when applying the currently available diffusive and convective options. Nevertheless, by implementing complex interventions, it may be possible to increase removal still further, e.g. by combining higher dialyser surface and dialysate flow with lower blood flow. Such a strategy results in an increase of protein-bound solute removal, without a change in urea removal. Although the procedure is complex and costly, this analysis demonstrates that there are still ways to improve removal, but also that our current method of assessing dialysis adequacy by evaluating removal of urea does not capture all aspects of dialysis removal, and may miss differences in the efficacy of protein-bound solute removal, for example.

Another approach that has recently gained renewed interest is the use of extracorporeal sorbents. Sorbent strategies were used previously in the RedyR system, which was abandoned, however, basically due to the release of sodium and aluminium. There now appears to be a revival in sorbent techniques, in the hope of reducing the use of dialysate and the volume of dialysis machines. A proof-of-concept study has been conducted, in which a combination of plasma separation and adsorption was assessed – a strategy which is essentially used nowadays against liver failure. The method was proven to be highly efficient in removing protein-bound solutes, but unfortunately the study had to be stopped prematurely because of coagulation problems. Other sorbent systems are currently under evaluation, in Europe in the context of the Neokidney project of the Dutch Kidney Foundation, which emanated in the development of sorbent coated dialysis membranes and sorbent systems for potassium and phosphate.

Other approaches that are still at an experimental stage are: sorption on metal beads which are then removed magnetically, regenerated, and recirculated; bioartificial kidney, combining classical extracorporeal removal to living tubular cells seeded on the dialysis membrane, the cells being added to increase removal capacity into the dialysate; and modifying the physical conditions of the plasma, e.g. by infusing hypertonic sodium that is removed afterwards via the dialysate, or by sending electric charges through the extracorporeal blood stream.

However, apart from trying to improve extracorporeal removal, there may also be other ways of improving uraemic toxin removal, e.g. by influencing intestinal uptake and urinary excretion. These two options have only recently attracted attention. In the last part of this presentation, we will try to summarize the knowledge that is emerging in these areas.

The intestine as a source of uremic toxins has recently attracted considerable interest. Several solutes are generated from protein breakdown products that are metabolised by the intestinal microbiota and then absorbed. In a study comparing serum metabolites, including several toxins, in the plasma of dialysis patients with and without colon, patients without a colon had up to one hundred-fold lower concentrations. Other studies showed a shift in uremia of the composition of intestinal microbiota towards germs that are more prone to generate uremic toxins. This offers a rationale for interventions that would favourably influence the composition of intestinal microbiota, such as administration of probiotics, prebiotics or synbiotics. However, the quality of studies assessing their impact on uremic toxin concentration was not always convincing until recently, especially when the studies had been undertaken in patients with chronic kidney disease. One recent study showed a lower urinary excretion and thus intestinal generation of indoxyl sulphate in subjects on a vegetarian diet, as compared to omnivores. A randomized controlled trial (RCT) in CKD patients could demonstrate an impact of synbiotics on serum indoxyl sulphate and p-cresyl sulphate. It is noteworthy that, in both studies, the effect on indoxyl sulphate was not perfectly paralleled by the effect on p-cresyl sulphate. Although KremezinR (AST-120), a sorbent with the capacity to capture indoxyl sulphate and probably also other protein-bound uremic toxins, seemed promising for preserving renal function in a number of smaller Japanese RCTs, larger studies subsequently conducted were unable to confirm these conclusions.

A second factor with potential impact is residual renal function, which, even in dialysis patients, is associated with better survival and lower uremic toxin concentration. At present, efforts are essentially focusing on preserving kidney function in the pre-dialysis population, but some of these interventions may be influential at the dialysis stage as well. Both cardiovascular disease and progression of kidney failure seem to be linked to Nuclear Factor- $\kappa$ B (NF $\kappa$ B) and monocyte chemoattractant protein-1 (MCP-1 or CCL-2). Current efforts by the scientific community are aimed at developing blockers of these pathways, and although some of the drugs emerging appeared to be unsuccessful (e.g. Bardoxolone), the way remains open for alternatives. *(continued on page 19)*



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Katowice, Poland  
President ERA-EDTA

# Why is hypertension so prevalent in systemic diseases?

*The roles of inflammation, physical inactivity and medication*

Arterial hypertension is frequently found in patients with systemic diseases like rheumatic disease, psoriasis, vasculitis or lupus erythematosus [1]. For example, among patients with rheumatic disease (RD) the prevalence of arterial hypertension (estimated to 52-73 %) is almost double that in the general population. Conversely, the proportion of patients with well-controlled blood pressure is much lower than in the general population (15 % vs. 30 % respectively). Additionally, both cardiovascular (CV) morbidity and mortality are higher in patients with RD compared to controls, which is only partially explained by the traditional CV risk factors [1].

It has been documented that patients with RD and other systemic diseases are characterized by high CV risk similar to that observed in patients with diabetes mellitus and chronic kidney diseases. This increased prevalence of hypertension in patients with systemic diseases like RD can be explained by several factors: systemic and low-grade inflammation, physical inactivity and medication (for example, nonsteroidal anti-inflammatory drugs [NSAIDs], corticosteroids or cyclosporine A) used in order to reduce the activity of the disease and its symptoms.

Inflammation plays an important role in the pathogenesis of excessed CV risk. Increased concentration of high-sensitivity C-reactive protein (hsCRP) representing systemic inflammation are characteristic of patients with systemic diseases like RD. Low-grade systemic inflammation can lead to hypertension through several mechanisms: (a) reduction of nitric oxide production in endothelial cells leading to vasoconstriction, (b) increased production of endothelin-1, and (c) platelet activation. Moreover, CRP is able to upregulate the expression of angiotensin type-1 (AT1) receptors, thus which directly activates the renin-angiotensin system (RAS) [2]. All above mentioned factors participate in the pathogenesis of increased systemic vascular resistance and arterial hypertension (Figure 1).

Patients with systemic diseases like RD are characterized by reduced physical activity, which may be caused by chronic pain, accompanied by the joint and muscle damage. Such a

condition may lead to overweight or obesity in some patients, and, secondarily to hypertension. In addition to these pathophysiological processes, several drugs used in systemic diseases (NSAIDs, glucocorticoids (GC), cyclosporine A and others) can also increase blood pressure and inhibit the effects of antihypertensive drugs such as diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB).

Nonselective NSAIDs and coxibs are frequently used in patients with systemic diseases like RD. Prolonged treatment with NSAIDs may cause an average of 5 mmHg elevation in systolic blood pressure. The highest increase in blood pressure was observed during treatment with piroxicam, indomethacin and naproxen [3]. The blood pressure increasing effect of nonselective NSAIDs was more pronounced in hypertensive than in normotensive patients. Possible background mechanisms can be: (a) salt and water retention by decreased prostaglandin production (b) increased peripheral vascular resistance by increasing endothelin-1 synthesis and (c) inhibition of vasodilatory prostaglandin synthesis (especially PGE<sub>2</sub>) [4]. Several studies have revealed that coadministration of nonselective NSAIDs with diuretics, beta-blockers, ACE inhibitors and angiotensin II receptor blockers (ARBs) results in attenuation of the antihypertensive effect. Interestingly, this effect cannot be observed with calcium channel blockers (CCBs) [5].

The blood pressure elevating effect of prolonged GC treatment has been known for a long time. Use of even a moderate dose of prednisolone (> 7.5 mg / day) for more than 6 months elevates blood pressure and increases the incidence of hypertension. Cyclosporine A is known to cause hypertension, and it is contraindicated in patients with severe, uncontrolled hypertension. There are different hypotheses to explain cyclosporine-induced hypertension: (a) by enhancing endothelin-related vasoconstriction, (b) by reducing nitric oxide and suppressing prostacyclin production, and (c) by reducing the glomerular filtration rate and causing sodium retention. Cyclosporine-induced hypertension should be treated with CCBs (diltiazem and verapamil are preferred, however they can increase blood level of cyclosporine A). Reduction of the dose or withdrawal of cyclosporine is recommended in those patients where the hypertension becomes resistant to antihypertensive therapy.

No evidence exists to suggest any impact on blood pressure, or on the effects of antihypertensive drugs during treatment

with such agents as TNF-alpha inhibitors, rituximab, anakinra or abatacept.

In conclusion:

1. Hypertension is frequently present in patients with rheumatic diseases, psoriasis and other systemic diseases.
2. Inflammation plays an important role in the pathogenesis of hypertension and metabolic disorders in these patients.
3. Cardiovascular mortality is higher in patients with systemic diseases than in general population.
4. Antiinflammatory drugs may interfere with the treatment of hypertension.
5. Patients with systemic diseases should be considered as high-risk patients and therefore should remain under the special care of both the cardiologist and the nephrologist. ■

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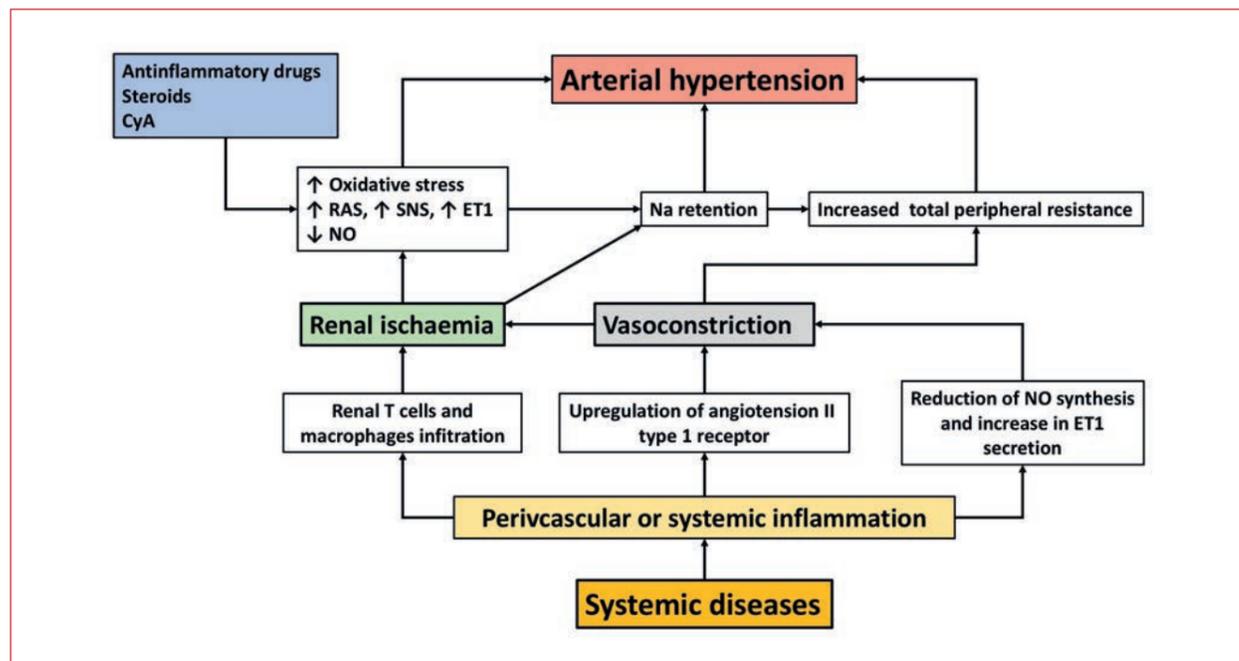
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## Session

**EURECA-M/CME 3**

**A preview of the future in cardiovascular risk management in CKD**

**TODAY, 09.00 – 12.15  
HALL B**



**Figure 1: Interaction between peripheral or systemic inflammation and arterial hypertension.** © Więcek

ET1 = Endothelin 1, NO = Nitric oxide, CyA = Cyclosporine A, RAS = Renin-Angiotensin System, SNS = Sympathetic Nervous System

(continued from page 18) In conclusion, with the introduction of high-flux membranes and hemodiafiltration, extracorporeal dialysis strategies have reached a high level of efficiency, while excessively steep increases in removal are largely offset by rebound unless dialysis duration is extended. Future improvements may take the direction of sorbents allowing more compact and flexible dialysis systems. Other, highly technological, alternatives do not extend beyond the experimental stage at present. In future, we should start to consider decreasing the intestinal generation of uraemic toxins. Options include prebiotics, probiotics and synbiotics, but this issue needs further evaluation and studies which go beyond measuring toxin concentration and which are directed at hard outcomes. A final option is to preserve residual kidney function. ■



**MEHMET KANBAY**  
Istanbul, Turkey

# Renal congestion in heart failure: concept and impact on outcomes

*Understanding of the special relationship between the heart and the kidney*

The marriage between the heart and the kidney is particularly special. The heart is directly dependent on the kidneys for the regulation of salt and water in the body and vice versa the kidneys are directly dependent on blood flow and blood pressure generated by the heart. The bidirectional interaction of these organs can create a nexus of deterioration in both. The umbrella term 'cardiorenal syndrome' is used to define disorders of the heart and kidneys,

in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction or failure in the other.

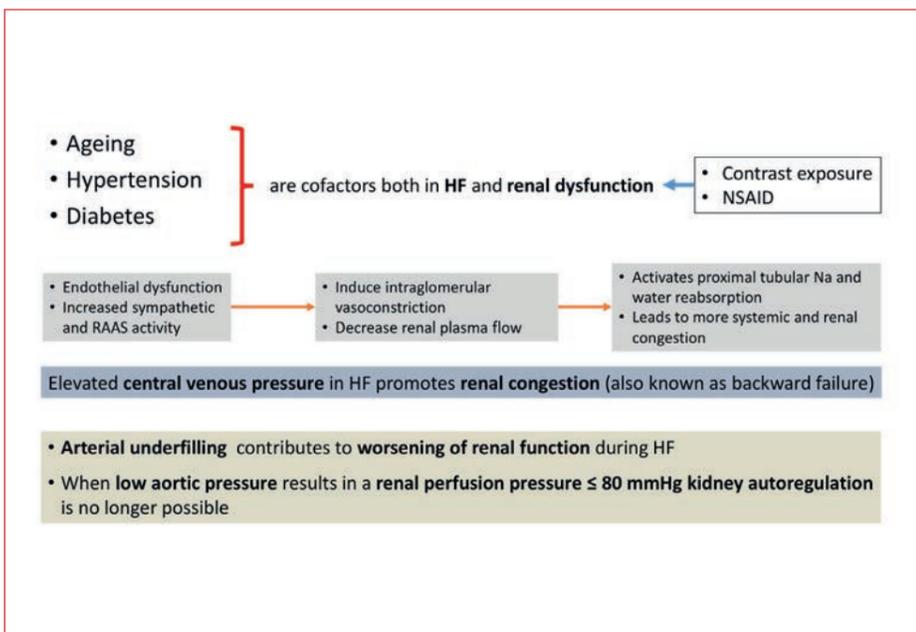
Cardiac disease is often associated with worsening renal function and vice versa. The coexistence of cardiac and renal disease significantly increases mortality, morbidity and the complexity and cost of care. Hospitalizations due to congestive heart failure are increasing steadily despite advances in medicine. Patients hospitalized for worsening heart failure are at high risk of mortality both in hospital and within the months following discharge.

Kidney dysfunction is associated with adverse outcomes in heart failure patients. Recent evidence suggests that both deterioration in kidney function and renal congestion

are important prognostic factors in heart failure. Almost all studies have found that even a small, as low as 0.2 mg/dL, increase in serum creatinine (defined as worsening renal function) is associated with poor outcomes, including increased mortality in both inpatients and outpatients.

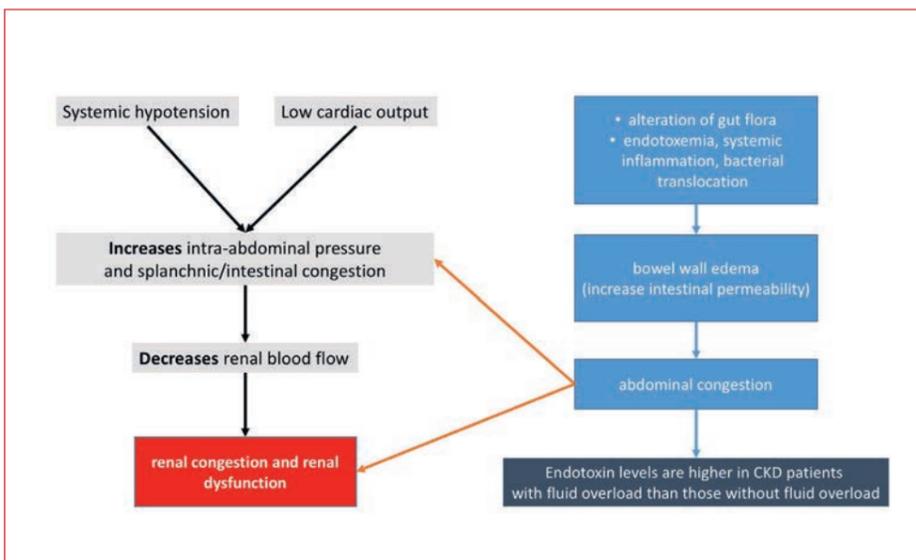
Impaired renal function and congestion in heart failure represent much more than simply a reduction in glomerular filtration rate. The cause of renal congestion and worsening of renal function is multifactorial. Renal congestion in heart failure mainly results from low cardiac output (forward failure), tubuloglomerular feedback, increased intra-abdominal pressure or increased venous pressure (venous congestion) and reduced renal perfusion. In addition, increased activity of the renin-angiotensin-aldosterone and the sympathetic nervous systems, oxidative stress and inflammation also play important role (Figures 1, 2 and 3).

Regardless of the cause, renal congestion and worsening renal function are associated with greater morbidity and mortality in patients with heart failure. The impact on outcomes of renal decongestion strategies that do not compromise renal function should be explored in heart failure. Adequate control of congestion with simultaneous improvement/preservation of kidney function has been proposed as a central goal of patient management in heart failure. Currently, water and salt restriction, diuretic therapy and ultrafiltration in diuretic-resistant patients are the mainstays of treatment in patients with decompensated heart failure. We require novel diagnostic markers to identify early renal damage and renal congestion, and allow monitoring of treatment response in order to avoid severe worsening of renal function. In addition, there is an unmet need for evidence-based therapeutic management of renal congestion and worsening renal function. ■



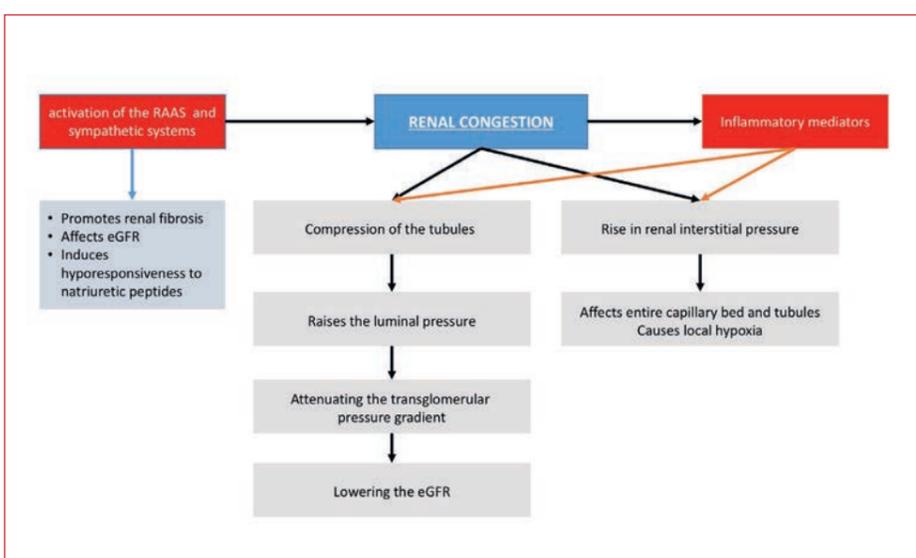
**Figure 1: Pathophysiology of Renal Congestion and Worsening Renal Function in Heart Failure**

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**Figure 2: Pathophysiology of Renal Congestion and Worsening Renal Function in Heart Failure**

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**Figure 3: What are the consequences of renal congestion?**

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## Session

**EURECA-M/CME 3**

**A preview of the future in cardiovascular risk management in CKD**

**TODAY, 09.00 – 12.15 HALL B**

# European Uremic Toxin (EUTox) Working Group of the ESAO and Endorsed Working Group of the ERA-EDTA

The mission of EUTox is to prevent vascular and kidney disease, in order to save lives and costs in the future. To that end, EUTox focuses on defining biomarkers that would allow early diagnosis of disease onset, identifying compounds that delay or halt disease progression, and

on improving therapeutic strategies aimed at the prevention of disease and disease progression. The Working Group is now composed of 24 European research institutes. In addition to its scientific work and joint projects, EUTox organizes regular meetings and CME courses.



Current chairmen of the working group are

**Angel Argiles, France**

**Joachim Jankowski, Germany**

Find more information at

<http://uremic-toxins.org>



**VERA JANKOWSKI**  
Aachen, Germany

## Posttranslational modifications of proteins and peptides

*Research by Vera Jankowski and her group points the way to novel biomarkers/mediators for CKD*

Posttranslational modifications of proteins and peptides have recently gained much attention, as they are involved in the pathogenesis of cardiovascular diseases (CVD). Posttranslational modifications are covalent changes of proteins or peptides that are altered either by proteolytic cleavage or by adding moieties to one or more aminoacids. This enhances their complexity with respect to regulation of activity state, subcellular localization, turnover and interaction with other cellular molecules. These modifications dramatically alter the physiologic and pathophysiologic properties of proteins. Several posttranslational modifications have been described in recent years: for example, advanced glycosylation, oxidation, nitrosylation, carbamylation or acetylation. Based on these descriptions, posttranslational modification proteins and peptides have gained attention as biomarkers and/or mediators of CVD and chronic kidney disease (CKD). More detailed analysis of these posttranslational modifications of plasma proteins are an urgent task in renal research to identify mechanisms that play a role in both the genesis and/or progression of CKD and CVD, since proteins are constantly being exposed to different plasma and tissue components under pathophysiologic conditions such as renal failure.

Recent progress in mass spectrometry has resulted in a dramatic increase in selectivity and sensitivity of these methods. Based on these advances, we are now able to reliably and reproducibly identify and quantify endogenous posttranslational modifications of proteins. Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry in particular allows an analysis of posttranslationally modified proteins, since MALDI mass spectrometry produces less multiply-charged ions compared to, for example, electrospray ionization, and mass spectrometry is not time-limited.

Against this background, a comprehensive method for the analysis of these posttranslational modifications was quite recently established for use in clinical diagnostics. The method was established by using albumin—the most abundant plasma protein in humans—isolated from CKD patients and healthy controls by chromatographic steps. Posttranslational modifications of albumin were identified by MALDI mass spectrometry after tryptic digestion by analyzing mass signal shifts of albumin peptides using pertinent mass-databases. It was demonstrated that albumin isolated from plasma of CKD patients, but not from healthy control subjects, was

specifically posttranslationally modified by guanidylation of lysines at positions 249, 468, 548, 565 and 588.

After identification of guanidylation as posttranslational modifications of albumin isolated from CKD patients, these modifications were quantified by mass spectrometry, and demonstrated a significant increase in the corresponding mass-signal intensities in CKD patients compared to healthy controls. The relative amount of guanidylation of lysine at position 468 in CKD patients was determined as  $63 \pm 32\%$ . The characterisation of the pathophysiologic impact of the posttranslational guanidylation on the binding capacity of albumin for representative hydrophobic metabolic waste products reveals a decreased binding capacity of albumin caused by in vitro guanidylation of albumin from healthy control subjects in a time-dependent manner. Binding of indoxyl sulfate (protein-bound fraction) decreased from  $82\% \pm 1\%$  of non-posttranslationally modified albumin to  $56\% \pm 1\%$  after in vitro guanidylation, whereas the binding of tryptophan decreased from  $20\%$  to  $4\%$ . The results are in accordance with the binding of indoxyl sulfate to albumin from healthy control subjects and CKD patients ( $88 \pm 3$  vs.  $74 \pm 10$ ,  $p < 0.01$ ). Thus, in vitro posttranslational guanidylation of albumin might have a direct effect on the binding capacity of hydrophobic metabolites like indoxyl sulfate and tryptophan.

The mass spectrometry-based method used was capable of characterizing posttranslational modification of proteins and demonstrating the pathophysiologic impact of a representative posttranslational modification of plasma albumin, and the data may help to elucidate the pathophysiologic role of protein modifications. However, this mass spectrometry-based method was highly time consuming and work intensive, and therefore this method is not appropriate for the use in large clinical studies. Therefore, the group of Vera Jankowski, PhD at the "Institute for Molecular Cardiovascular Research" (IMCAR) at the University Hospital RWTH Aachen (Germany), is developing alternative approaches to screen plasma protein for posttranslational modifications. Specific antibodies for the plasma protein of interest are immobilized by covalent coupling to activated affinity beads. The immobilized antibodies are incubated with the plasma samples of patients and controls. The adsorbed plasma proteins are released from the antibody by using an increased ion-strength, and the desalted proteins are analyzed by matrix-assisted laser desorption/ionization mass-spectrometry for posttranslational modification of the eluted proteins.

Vera Jankowski told us in an interview: "The method will be adaptable to high-throughput sample handling and automated mass spectrometric analysis and therefore suited for clinical studies, too." ■

## Session

**EUTOX/CME 7**

**Uraemia: is it only a toxin affair? The emerging concept of networking**

**TODAY, 09.00–12.15  
HALL M**

## Online

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**Introducing an integrative, network concept in uremic toxicity**

**ALBERTO ORTIZ**  
Madrid, Spain



**Uremia: is it only a toxic affair?**

**ROOS MASEREEUW**  
Utrecht, The Netherlands



**ALBERTO ORTIZ**  
Madrid, Spain

# Introducing an integrative, network concept in uremic toxicity

*Not every molecule that displays increased concentrations in uremia is a uremic toxin*

In the 19th century urea was the first retention solute shown to accumulate in kidney failure. Since then, it has been believed that uremic retention solutes account for the clinical manifestations of uremia. Uremic toxins are described as "solute normally excreted by the kidneys that are retained in chronic kidney disease (CKD) and interact negatively with biologic functions", and were thought to underlie the manifestations of end-stage kidney disease (ESKD). However, advances in renal pathophysiology and metabolomics have challenged this simple concept. It is now becoming evident that the kidney occupies a central place in the homeostatic network of the body and that kidney failure constitutes a 'network disease'.

The concept of a network disease originates from central nervous system diseases. Thus, schizophrenia has eluded characterization in terms of local abnormalities of brain activity, and is hypothesized to be a network disease affecting the collective 'emergent' working of the brain. According to Wikipedia, "in philosophy, systems theory, science, and art, emergence is a process whereby larger entities, patterns, and regularities arise through interactions among smaller or simpler entities that themselves do not exhibit such properties. Life as studied in biology is commonly perceived as an emergent property of interacting molecules as studied in chemistry." In this sense, kidney failure is a network affecting the collective, 'emergent' working of the body. Accumulation of certain solutes or a deficiency in others disrupts the normal interaction between organs and systems, so promoting disease.

The clinical consequence of the conventional uremic toxin concept is that we should improve excretion of small solutes, which gave rise to the dialysis concept. However, knowledge about the different functions of the kidneys and the sequence of events secondary to reduced kidney function allow us to update the concept of uremic toxins. This update

has the potential to impact on the therapeutic approach to the consequences of CKD. We now propose an updated conceptual framework that provides guidance to potential therapeutic approaches to the clinical consequences of CKD. First, the spectrum of uremic retention solutes and uremic toxins should be expanded to include those that accumulate as a consequence of decreased degradation by the kidneys or increased synthesis or gut absorption. They are not just retention solutes because of reduced excretion. Some solutes may accumulate as a consequence of decreased degradation: for example, small proteins. As a clinical consequence, we should improve excretion of middle-molecular weight solutes. This links to the high-flux dialysis concept as a surrogate for increasing degradation. Some solutes may accumulate as a consequence of increased synthesis. As a therapeutic consequence, we may design approaches to inhibit/decrease their synthesis. In this regard, measured levels in the circulation may underestimate the biological consequences, since concentrations may be higher at site of synthesis or cell membrane. The increased synthesis may be a direct consequence of accumulation of: classical, known uremic toxins such as parathyroid hormone (PTH) following phosphate or carbamoylated proteins following urea, or may be the result of changes in microbiota as in, for example, the increased synthesis of trimethylamine-N-oxide (TMAO) from oral L-carnitine; or due to known or unknown/uncharacterized triggers, such cytokines. Lastly, for some solutes it is unknown whether synthesis is increased or degradation/excretion decreased.

Some solutes may accumulate as a consequence of increased absorption in the gut. As a clinical consequence, we may design therapies to inhibit/decrease absorption. Other uremic toxins may not be reflected in serum levels and we need functional assessment; for example, high-density lipoprotein (HDL) in uremia is modified so that it behaves as a proinflammatory molecule and loses its protective properties.

In addition, for some molecules the issue is not increased, but rather decreased level in uremia, and injury or dysfunction occur as a consequence of decreased levels. We may term these inverse uremic solutes (similar to the concept of inverse acute phase reactants) or uremic benefitins (as opposed to toxins). The concentration/activity of these molecules is decreased as a consequence of kidney dysfunction, either because of

lower synthesis or increased losses, for example, the concentration of hydrogen sulfide falls in between dialysis sessions and increases after dialysis, indirectly suggesting an effect on concentration by uremic toxin removal. The low levels of these benefitins cause injury.

Lastly, primary and secondary uremic toxins or benefitins may be recognized. Changes in the concentration of primary uremic toxins or benefitins are the direct consequence of kidney dysfunction; for example, phosphate accumulation. By contrast, the concentration of secondary uremic toxins or benefitins may change in response to the accumulation of primary uremic toxins (for example, increased fibroblast growth factor 23 [FGF23] levels being secondary to phosphate accumulation, decreased calcitriol levels favoring the increase in PTH). This classification has therapeutic consequences: every effort should be made to identify primary uremic toxins or benefitins, as an adequate control of their concentrations will automatically result in correction of secondary uremic toxins levels.

Any attempt to correct the adverse effects of a given uremic toxin requires a correct understanding of the true uremic toxins. For many solutes named as such, the ability to induce adverse effects has not been demonstrated in vivo. Final proof of concept can only be obtained if (selective) removal/supplementation results in an improvement of hard outcomes (in controlled trials). Alternatively, one might be satisfied with high quality in vitro/animal studies together with observational studies showing correlation with hard outcomes (for example, protein-bound uremic toxins). However, we should be aware that benefitins may be either increased and help mitigate the clinical consequences of uremia, or decreased to become a causative contributor to uremic symptoms. In this regard, not every molecule that displays increased concentrations in uremia is a uremic toxin. ■

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## WIKIPEDIA – The Free Encyclopedia

### Emergence

In **philosophy, systems theory, science, and art**, **emergence** is a process whereby larger entities, patterns, and regularities arise through interactions among smaller or simpler entities that themselves do not exhibit such properties.

Emergence is central in theories of **integrative levels** and of **complex systems**, (...)

**Life** as studied in **biology** is commonly perceived as an emergent property of interacting molecules as studied in **chemistry**, (...)



**Figure 1: Emergence** © Text by wikipedia.org, Keyword: emergence / Photo taken and supplied by Brian Voon Yee Yap. Cathedral Termite Mounds in the Northern Territory. CC BY-SA 3.0 wikimedia.org



**ROOS MASEREEUW**  
Utrecht, The Netherlands

## Uremia: is it only a toxic affair?

*The renal tubular handling of uremic metabolites*

years, thorough optimization of the semipermeable material used in these dialysis devices and optimization of the design have pushed the therapy towards daily clinical practice [4].

Dialysis therapy greatly contributes to an improved prognosis of patients with kidney failure, but the treatment cannot correct the full spectrum of uremic toxicity. It was Homer W. Smith in his "From Fish to Philosopher" [5], who first suggested that the accumulating wastes (also termed uremic toxins) might be secreted rather than filtered, which explains the limitations of dialysis therapy. Inspired by the serious health problems faced by CKD patients that go beyond the kidneys, the nature of uremic solutes have been subject to extensive investigations. The ERA-EDTA-endorsed European Uremic Toxin Workgroup compiled a database of more than 150 substances found at higher concentrations in the plasma of patients with uremia as compared with normal individuals (<http://www.uremic-toxins.org/>) [6, 7].

Based on their chemical properties that affect their removal by dialysis, uremic toxins can be divided in three classes:

- Class 1 consists of small water-soluble solutes with a molecular weight of <500 Da such as urea, which can be easily removed using dialysis
- Class 2 contains the middle molecules (with a molecular weight > 500 Da), which can only be cleared using large-pore dialyzer membranes
- Class 3 is composed of the protein-bound uremic toxins.

In general, Class 3 solutes have a molecular weight smaller than 500 Da, but are difficult to remove by dialysis because of their high plasma-protein binding which greatly increases their molecular weight. The removal of the Class 3 compounds by the kidneys depends predominantly on renal tubular epithelial cells that are capable of shifting the bound fraction to the free fraction and facilitating their urinary ex-

cretion. For this, the proximal tubular epithelial cells (PTEC) of the kidneys in particular are equipped with multiple transport proteins with overlapping substrate specificities that vigorously cooperate in basolateral (interstitial) uptake and luminal (urinary) secretion [8]. Replacing this highly specialized tissue function is a large hurdle to overcome for treatment in nephrology, but recent advances in bioartificial kidney engineering are promising [9,10].

In the CME session, entitled "Uraemia: is it only a toxin affair?" organized by the European Uremic Toxin Workgroup the urinary excretion mechanisms for uremic toxins in PTEC, along with the state-of-the-art bioengineered renal tubule capable of replacing this excretory function will be discussed. It will become clear that complex problems associated with uremia warrant a transdisciplinary approach that unites research experts in the area of tissue engineering and renal regeneration with their colleagues in clinical nephrology. ■

Kidney disease is as old as humanity itself, but it is only since the last century that we have begun to better understand kidney functioning and the consequences of renal failure. The term uremia, which means urine poisoning (from the Greek for 'urine in the blood') was introduced in the 18th century when Drs Fourcroy and Vauquelin discovered urea in urine. They speculated that if urea is not 'separated' from the blood, excess might lead to specific disorders [1]. Blood urea is still being used as a measure of kidney function.

Over the years, innovative research in the field of nephrology has led to significant advances in the treatment of chronic kidney disease (CKD). The preferred treatment of patients with end-stage renal disease (ESRD) is obviously kidney transplantation. However, due to a shortage of donor kidneys, most patients have to undergo renal replacement therapy (RRT) with dialysis. This procedure, based on ultrafiltration of fluid and the diffusion of solutes across a semipermeable membrane, removes accumulating solutes such as urea from the circulation.

One of the first to report that urea could be dialyzed from urine through semipermeable membranes was Dr Thomas Graham (1805-1869) [2]. In 1945, Dr Willem Kolff introduced the first clinically functional hemodialysis machine for the treatment of uremia [3]. This device consisted of a rotating-drum kidney in a static open bath, with 20 meters of cellophane dialysis tubing wrapped around it. Over the last 70

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# ERA-EDTA Immunonephrology Working Group (IWG)



Current chairman of the working group is  
**Vladimir Tesar, Czech Republic**

Find more information at  
[www.era-edtaworkinggroups.org/en-US/group/immunonephrology](http://www.era-edtaworkinggroups.org/en-US/group/immunonephrology)

The Immunonephrology Working Group (IWG) of the ERA-EDTA was founded in 2009 to foster research, teaching, communication and education in the field of immune system dysregulation. This includes glomerular, tubular, vascular immune-mediated renal diseases, immune mechanisms in pathogen-

esis and progression of renal damage, as well as immune-mediated damage in kidney transplantation. The IWG promotes and organizes research in these fields, regular meetings to encourage scientific networking, and various CME courses focusing on educational themes.



**DAVID JAYNE**  
Cambridge, United Kingdom

Three sets of international guidelines for the diagnosis and treatment of lupus nephritis were published in 2012, including those by KDIGO, by a joint working party of the ERA-EDTA and the European League Against Rheumatism (EULAR), and by the American College of Rheumatology. They differed in emphasis and breadth, and a recent review has summarised their similarities and differences along with recently published national guideline statements (1). Renal biopsy remains the standard diagnostic procedure, supported by clinical, laboratory and serologic data. However, the validity of the ISN/RPS 2003 system for histological classification has been called into question due to its lack of association with renal outcomes and omission of tubular-interstitial and vascular features. A proposal for a new initiative, analogous to the Oxford classification for IgA nephropathy, has been made. Repeat renal biopsy studies have demonstrated the evolution of histological class and the maintenance of a

## Lupus nephritis

distinction between segmental and global lesions, although there appears to be no prognostic value of this distinction (Figure). Repeat biopsy studies have also highlighted the discrepancy between renal remission defined by loss of proteinuria when compared to histologic remission. This is of particular relevance when trying to judge whether a patient with persisting proteinuria is treatment refractory or not. Further randomised clinical trial evidence for the efficacy of tacrolimus-based induction regimens, either with glucocorticoids or the 'multitarget' approach with mycophenolate mofetil and glucocorticoids, has been published. A large Chinese randomised controlled trial by Liu et al (2) is worthy of note. If concerns over the long-term outcome and relapse risk of patients receiving this treatment are addressed, this is likely to influence future treatment guidelines. Also, most of the evidence has been derived from studies in Asia, and data from other ethnic groups is required.

The evidence for rituximab as an induction and steroid sparing agent has grown, although not based on further randomised trials. One study combined rituximab with mycophenolate mofetil, but without oral studies and reported good response rates. This observation requires confirmation and longer term follow-up. Rituximab continues to occupy a place in the guidelines for refractory disease, but there is a real need for better data. Randomised trials of other biologic agents, including ocrelizumab (anti-CD20), abatacept (CTLA4-Ig) and ataccept (soluble TACI receptor that inhibits BlyS and APRIL signalling), have either been negative or stopped due to safety con-

cerns. Ongoing trials include investigations into belimumab, the combination of belimumab with rituximab, anifrolimumab (anti-interferon alpha receptor), anti-CD40 ligand and anti-CD40, and a newer calcineurin inhibitor, voclosporin. By 'post-hoc' analysis of long-term clinical trial data, the optimum level of proteinuria to judge a 'complete response' has been defined as an albumin creatinine ratio of between 0.7 and 0.8 mg / mg, slightly higher than the current level of 0.5. Related studies have observed that urine sediment and haematuria do not add precision to complete response definitions and should not be used for this purpose. Lupus nephritis remains a challenging disease to manage with toxic drug combinations and a paucity of reliable biomarkers to guide optimal treatment. Over the last fifteen years, a considerable amount has been learned about how to perform clinical investigations with these patients, and this has also informed routine clinical management. Drugs currently under investigation will potentially be more effective and safer than our current regimens, and updating of consensus guidelines will be required. ■

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**YASAR CALISKAN**  
Istanbul, Turkey

IgA nephropathy (IgAN) is the most prevalent primary glomerular disease worldwide and an important cause of end-stage renal disease. The underlying pathogenesis of IgAN comprises the formation of immune complexes, including glycan-specific IgA1 or IgG antibodies and an aberrant glycosylation of IgA1 called galactose-deficient IgA1 (Gd-IgA1). Although kidney biopsy is the gold standard for diagnosis and the evaluation for treatment, it is invasive and has several serious complications. The measurement of novel biomarkers in plasma, serum or urine could be an alternative means of providing meaningful information for the diagnosis and prognosis of this glomerular disease. Recent years have been marked by dramatic progress in clarifying the genes and specific molecular

## Can biomarkers substitute for renal biopsy in IgA nephropathy?

*Encouraging progress, but novel technologies are not yet ready for clinical practice*

pathways involved in the pathogenesis of IgAN. These discoveries have stimulated the development of novel biomarkers and offer the prospects of non-invasive diagnosis and improved prognostication.

### Biomarkers for Diagnosis

Now, we do know that IgAN patients have high serum levels of Gd-IgA1, together with Gd-IgA1-specific IgG levels. The serum levels of Gd-IgA1 and anti-glycan antibodies directed against the hinge region of Gd-IgA1 represent the most promising candidate biomarkers for diagnosis. A lectin-based ELISA assay for circulating Gd-IgA1 demonstrates 90% specificity and 76% sensitivity for diagnosis of IgAN; thus it appears to be one of the best candidates for a new non-invasive diagnostic test. MicroRNAs, short noncoding RNA molecules that regulate gene expression, might have important roles in the pathogenesis and progression of IgAN. Of all miRNA biomarkers published in the literature, miR-148b has the most potential as a clinical biomarker, as it was validated in several different cohorts and platforms and has been shown to be

involved in regulating C1GALT1, a key player in the pathogenesis of IgAN. Recently, serum levels of the combined miRNA biomarker, let-7b and miR-148b were suggested as a novel, specific, and noninvasive biomarker to test the probability of an individual being affected by IgAN, so aiding clinicians in diagnosis. However, in current practice the 'gold standard' for diagnosing IgAN is still biopsy of renal tissue, and a less invasive procedure for diagnosis is as yet unavailable.

### Biomarkers for Prognosis

The clinical course of IgAN ranges from long-term stable renal function with minimal proteinuria and microscopic hematuria to rapidly progressive glomerulonephritis with crescents on renal biopsy that progresses to end-stage renal disease in a very short time. This variability in clinical course anticipates different treatment options. Clinical follow-up of the disease is based upon indirect markers of renal function like proteinuria, serum creatinine and glomerular filtration rate (GFR). These markers are not specific for IgAN and the lack of disease-specific markers hinders the standardization of patient

A symposium sponsored by Bayer

## Sunday 22 May, 18:45 –19:45 Hall N, Level 1

Adverse cardiovascular events are the leading cause of death in patients with diabetic kidney disease (DKD). In this Bayer-sponsored symposium, a distinguished panel of experts will examine the link between renal and cardiovascular disease, and explore the benefits of current and emerging therapies in reducing renal and cardiovascular risk in patients with DKD. Please join us for an informative and stimulating meeting.



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### Welcome and introduction

Chair: Hermann Haller (Germany)

### Cardiovascular outcomes in patients with diabetic kidney disease: epidemiology and pathophysiology

Patrick Rossignol (France)

### Emerging therapies for reducing renal and cardiovascular risk in patients with diabetic kidney disease

Peter Rossing (Denmark)

### Summary and close

Hermann Haller

A light snack will be served from 18:45  
We look forward to seeing you at the symposium

L.AT.MA.04.2016.4039

follow-up and treatment. The Oxford Classification of IgAN identified mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), and tubular atrophy / interstitial fibrosis (T) as independent predictors of outcome. The tubular atrophy / interstitial fibrosis score has been the most consistently validated across different cohorts and ethnicities, and represents a reliable histologic predictor of poor renal outcome. However, in the large majority of IgAN patients, clinical or histologic indicators perform weakly on an individual basis. Thus, several investigators have attempted to combine these two approaches. Barbour et al have recently used 3 IgAN patient cohorts to assess the predictive value added to clinical data by the MEST score. Probably the most important finding of this study is that adding MEST score to estimated GFR, proteinuria, and blood pressure at baseline

#### IgAN Biomarkers

##### Genetic biomarkers

- HLA-DQ / DR locus (rs7763262-C risk allele)

##### Other SNPs:

- rs17019602 [G], rs6677604 [G], rs9275224 [G], rs2856717 [T], rs9275596 [T], rs2071543 [G], rs1883414 [C], rs2738048 [T], rs10086568 [A], rs4077515 [A], rs11150612 [A], rs11574637 [T], rs3803800 [A], rs2412971 [G]

##### Histopathological risk classification

- Oxford / MEST Classification (with crescents)

##### Serum biomarkers

- Galactose-deficient IgA1 (Gd-IgA1)
- Antigliyan antibodies (Gd-IgA1-specific IgG)
- sCD89 levels
- Serum levels of miRNAs, let-7b and miR-148b
- Soluble form of IL-2R protein (sIL-2R)
- AOPP (oxidative stress)

##### Urine biomarkers

- Interleukin 6
- Podocalyxin
- IgA-IgG complexes
- sTFR
- Membrane attack complex (MAC; C5b-9)
- N-acetyl-beta-D-glucosaminidase (NAG)

Table 1: Potential Biomarkers for IgAN © Caliskan

enabled the model to perform as well as models based on 2-year clinical follow-up data alone. This is currently seen as the best clinical model, but of course is not particularly practical in real-life scenarios. As the prognosis of IgAN is partly determined by the time point of diagnosis, there is an urgent need for reliable, noninvasive biomarkers that might be able to detect subclinical IgAN, estimate the degree of disease activity and assess the efficacy of treatment. Serum levels of Gd-IgA1, together with Gd-IgA1-specific IgG levels, have also been proposed as good candidate biomarkers for the prediction of IgAN prognosis. Utilizing a lectin-based ELISA assay, a recent study from China suggested that a high level of Gd-IgA1 at the time of diagnosis was associated with a faster rate of renal function decline. These observations are promising, but will require replication in independent cohorts. Additionally, a lectin-based ELISA assay for circulating Gd-IgA1 has been difficult to standardize, and for this reason it has not yet been introduced in routine clinical practice. A novel Gd-IgA1 Assay Kit measuring serum Gd-IgA1 levels with a lectin-independent method will be released on to the market soon. Urinary miRNA levels could also potentially serve as biomarkers for diagnosing and monitoring IgAN; however the data is still limited. Although these methods represent meaningful progress in the search for new biomarkers that may substitute for renal biopsy in IgAN, there are still a number of challenges. Most of the suggested biomarkers are not specific to IgAN, prospective validation studies in different cohorts are still lacking and novel technologies including proteomics and miRNAs are not yet available in routine clinical practice. In conclusion, if I am asked whether biomarkers can substitute renal biopsy in IgAN, my answer is not "no", but "not yet"! ■

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### ANCA-associated vasculitis

**VLADIMÍR TESÁR**  
Prague, Czech Republic

## Session

### IWG/CME 1

## Diagnostics and treatment of glomerular disease

**TODAY, 09.00 – 12.15  
HALL E**



**VLADIMÍR TESAR**  
Prague, Czech Republic

## Beyond KDIGO guidelines: when should we use rituximab?

### *Treatment of ANCA-associated renal vasculitis*

Until recently, the only effective induction treatment of active renal antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) was the combination of oral or pulsed cyclophosphamide with initially high-dose and gradually tapered corticosteroids, followed by maintenance treatment usually with azathioprine and low-dose corticosteroids for at least 2 years. This treatment was generally highly effective, inducing remission in more than 90% of patients, but with a relatively high rate of relapses (50% of patients relapsing within 5 years) and especially with chronic toxicity related to high cumulative dose of cyclophosphamide (secondary malignancies, gonadal failure) and inability to avoid corticosteroids (cataracts, osteoporosis, obesity, secondary diabetes, etc.).

In 2010, the RAVE study demonstrated that one cycle of rituximab (given in the so-called lymphoma protocol) is similarly effective as cyclophosphamide in inducing remission in newly diagnosed AAV and more effective than cyclophosphamide in patients with relapses of AAV (remission induced in 67% vs. 42% of rituximab and cyclophosphamide-treated patients, respectively). In the small RITUXVAS study, rituximab given with only two pulses of cyclophosphamide was similarly effective as a full course of cyclophosphamide in patients with severe renal vasculitis. KDIGO guidelines published in the same year suggested that rituximab could be used as an equipotent alternative to cyclophosphamide as an induction treatment of active ANCA-associated vasculitis.

Since then, long-term data from RAVE have demonstrated that, in terms of prevention of relapses, a single course of rituximab without maintenance treatment is similarly effective as 18 months induction-maintenance treatment

with cyclophosphamide followed by azathioprine. Long-term data from RITUXVAS also confirmed that the outcome for patients initially treated with rituximab (and only two cyclophosphamide pulses) is similar to that in patients who received standard induction treatment with pulsed cyclophosphamide.

It has, however, become apparent that, without adequate maintenance treatment, patients initially treated with rituximab are also prone to relapses (much more frequently in anti-PR3 compared to anti-MPO patients).

Recently published results of the randomized controlled MAINRITSAN trial, which compared maintenance treatment with rituximab and azathioprine in newly diagnosed patients with AAV, found that within 2 years the relapse rate of rituximab-treated patients was much lower than in those treated with azathioprine (5% vs. 29%, respectively). Rituximab thus seems to be the most effective available maintenance treatment of AAV. Although patients remain relapse-prone after rituximab withdrawal even after 2 years of rituximab maintenance treatment, the relapse rate seems to be much lower than in rituximab-naïve patients. New data from MAINRITSAN suggest that the quality of life of patients treated with rituximab may also be better than in azathioprine-treated patients. The currently ongoing MAINRITSAN2 study is comparing preemptive rituximab maintenance treatment with rituximab treatment based on B-cell repletion and ANCA titers. Another ongoing trial (RITAZAREM) is comparing rituximab and azathioprine maintenance in patients with relapses of ANCA-associated vasculitis.

What should be the impact of the newly available data on our approach to the treatment of patients with AAV? According to the guidelines of the British Society of Rheumatology, we can treat patients with AAV either with cyclophosphamide or rituximab induction and either with azathioprine or rituximab maintenance. In my opinion, this attitude is a bit conservative because we currently have good data demonstrat-

ing that rituximab should be preferred to cyclophosphamide in patients with major relapses of AAV. Possibly this should also be considered as a first-line maintenance treatment, at least in patients treated with rituximab induction (mostly relapsing patients who already relapsed on azathioprine).

Using rituximab as first-line treatment in patients with newly diagnosed AAV is still a somewhat controversial issue, as one cycle of cyclophosphamide is similarly effective and much less expensive. With the decreasing price of rituximab we can expect that the proportion of new patients treated primarily with rituximab will increase. The use of rituximab in AAV is already on the rise, and rituximab as a first-line treatment seems to be used more frequently by rheumatologists compared to nephrologists (who are probably generally less experienced with any biologic treatment), and more frequently in the USA compared to Europe. In my opinion, rituximab could be preferred in young patients with AAV to avoid unnecessary gonadotoxicity. On the other hand, we must be always aware that, although rituximab is generally well tolerated with a relative low rate of infectious complications (at most comparable to other immunosuppressive drugs) and infusion reactions, very rare but serious complications may occur: for example, progressive multifocal leukoencephalopathy (PML), thromboses, serum sickness, or pulmonary fibrosis.

The efficacy of rituximab in patients with severe renal vasculitis (serum creatinine at presentation > 500 µmol/l) is also not well documented and we definitely need more data. Although newer observational studies suggest that rituximab is also effective in granulomatous complications of AAV, including pulmonary or orbital granulomas, bronchial stenoses seem to be non-responsive to rituximab in a similar way to any other immunosuppressive treatment.

New EULAR/ERA-EDTA guidelines on the management of AAV will be soon published and will guide us, at least before the KDIGO guidelines on glomerulonephritis are updated. ■

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# ERA-EDTA Working Group on Inherited Kidney Disorders (WGIKD)



Current chairman of the working group is  
**Olivier Devuyst Switzerland**

Find more information at  
[www.era-edtaworkinggroups.org/en-US/group/wgikd](http://www.era-edtaworkinggroups.org/en-US/group/wgikd)

Inherited kidney diseases are a severe physical and psychological burden for the patients concerned – often children and their families. It is immensely important, therefore, to generate and disseminate new scientific knowledge about the causes, mechanisms and possibly about new treatments for in-

herited nephropathies. The aims of the WGIKD are to promote research, address the need for epidemiological data and registries, facilitate the dissemination of knowledge to health care providers, patients and their families, and to organize specific meetings and CME courses.



**FRANCISCO J. ARJONA**  
Nijmegen, The Netherlands

## Identification and functional characterization of new magnesiumotropic genes

urate renal Mg<sup>2+</sup> handling in animal models was facilitated. The establishment of these techniques allowed elucidation of the physiologic relevance in health and disease of new candidate genes that were postulated to play a role in renal Mg<sup>2+</sup> reabsorption. These innovative aspects for nephrology research were related to the key objectives of my project, namely:

- To establish zebrafish techniques to study defects in renal Mg<sup>2+</sup> reabsorption in vivo
- To identify new genes that, when dysfunctional, lead to impaired renal Mg<sup>2+</sup> reabsorption.

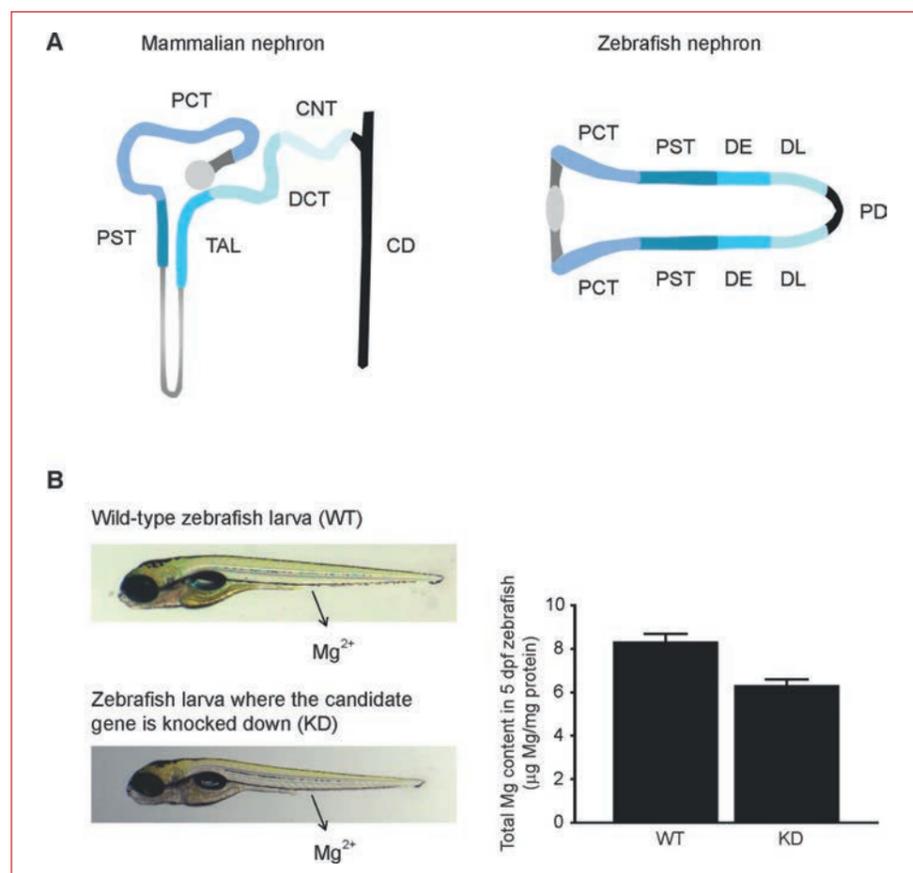
### Zebrafish techniques to study defects in renal Mg<sup>2+</sup> reabsorption in vivo

To date, suitable mammalian animal models to study renal Mg<sup>2+</sup> transport in vivo in health and disease have been lacking. Current and traditional vertebrate models (rodents) used to study these renal diseases are time-consuming to develop, not always easily accessible or simply lacking. Consequently, implementation of a more applicable vertebrate model is essential. In this respect, zebrafish provide an excellent vertebrate model to elucidate and characterize the (patho)function in vivo of hereditary (mutated) genes in the context of renal physiology. Specifically, the possibility of performing re-

Magnesium (Mg<sup>2+</sup>) is an essential cation that plays a paramount role in many physiologic processes including neuromuscular excitability, muscle contraction, myocardial metabolism and control over cell permeability. Consequently, systemic Mg<sup>2+</sup> imbalance results in phenotypic manifestations affecting essential organs that sustain life, namely the brain and the heart. Clinically, disturbances in Mg<sup>2+</sup> homeostasis are diagnosed after the determination of Mg<sup>2+</sup> concentrations in serum <0.7 mmol/L, a condition termed as hypomagnesemia. Conspicuously, hypomagnesemia is noted in approximately 15% of hospitalized patients, and the incidence may rise above 60% in intensive-care unit patients.

Mg<sup>2+</sup> homeostasis is primarily regulated by renal reabsorption involving a combination of paracellular and transcellular epithelial transport pathways. Within the nephron, the distal convoluted tubule (DCT), where transcellular reabsorption of Mg<sup>2+</sup> occurs, plays a paramount role in the maintenance of the systemic Mg<sup>2+</sup> balance. Although only 10% of the filtered Mg<sup>2+</sup> is reabsorbed in the DCT, this segment determines final Mg<sup>2+</sup> excretion into the urine, since no Mg<sup>2+</sup> reabsorption takes place beyond the DCT. Therefore, it is not surprising that most genetic causes of hypomagnesemia are associated with impaired DCT Mg<sup>2+</sup> handling. In the DCT, the apical entry pathway for Mg<sup>2+</sup> is formed by the Mg<sup>2+</sup> channel TRPM6. However, the molecular identity of other Mg<sup>2+</sup> transporters and most of the Mg<sup>2+</sup> regulatory proteins remains elusive to date. Because of this insufficient knowledge of renal Mg<sup>2+</sup> reabsorption in the DCT, many hospitalized patients with inherited or acquired hypomagnesemia remain without a clear genetic diagnosis and consequently lack personalized treatment. In detail, knowledge of the molecular players controlling Mg<sup>2+</sup> reabsorption in the DCT is key to elucidating the genetic etiology of drug-induced and inherited hypomagnesemia caused by renal Mg<sup>2+</sup> wasting, to identifying the link between hypomagnesemia and chronic diseases, and to designing potential treatments for hospitalized patients by establishing a new target for drug development.

Through the research developed with the Impulsion Grant from the Working Group on Inherited Kidney Disorders (WGIKD), advanced training in specific techniques to eval-



**Figure 1: The kidney (pronephros) of zebrafish larva is used as a model to identify and characterize potential magnesiumotropic genes.** © Arjona

(A) Zebrafish nephrons in larvae possess similar segment organization patterns as a mammalian nephron. In the zebrafish nephron, the following segments are distinguished: proximal convoluted and straight tubules (PCT and PST respectively); the distal early tubule (DE), equivalent to the mammalian thick ascending limb of the loop of Henle (TAL); the distal late tubule (DL), equivalent to the mammalian distal convoluted tubule (DCT); and the pronephric duct (PD), equivalent to the mammalian collecting duct (CD). Of note, zebrafish nephrons do not possess water-permeable segments (descending limb of the loop of Henle) since they are hyperosmotic with respect to the surrounding medium. The main connecting tubule (CNT) function (transcellular Ca<sup>2+</sup> reabsorption) is located in the skin of zebrafish larvae. (B) As zebrafish do not eat (they rely on absorption of the nutrients contained in the yolk) and do not drink (they are hyperosmotic) in the larval stage, differences in total Mg content between individual zebrafish larvae reflect differences in renal Mg<sup>2+</sup> (pronephric) losses as the pronephros is the only excretion route for Mg<sup>2+</sup>. When a DCT gene involved in (transcellular) Mg<sup>2+</sup> reabsorption is knocked down in zebrafish larvae, this results in a lower total Mg content, which correlates with a higher renal Mg<sup>2+</sup> wasting compared to wild-type larvae.

verse genetics approaches in zebrafish embryos and larvae by means of morpholino-knockdowns constitutes a fast and bona fide methodology to establish gene function in health and disease, compared with mammalian models. Additionally, the nephrons of the embryonic and larval zebrafish (pronephric) kidney are analogous to the nephrons of the mammalian (metanephric) kidneys, in terms of ion channel and transporter expression, function and segmental organization (Figure 1A).

Moreover, the hyperosmotic nature of zebrafish and freshwater fish in general respect to the surrounding medium provides a system whereby transcellular ion transport processes in the kidney are more prominent than paracellular transport processes driven by water. This particular physiologic feature of zebrafish can be used to advantage to detect fine disturbances in transcellular Mg<sup>2+</sup> transport in the kidney. The conspicuously high amino acid identity (usually >70% for the whole protein, reaching >95% for key functional domains) between zebrafish pronephric proteins and their human counterparts allows the application of phenotype rescue experiments with

human wild-type and mutant orthologs. This methodology has important implications for the extrapolation of findings from zebrafish to humans and the delineation of the pathofunction of specific mutations in kidney genes *in vivo*.

In this lecture, the zebrafish model will be presented as an excellent system in which to interrogate the conserved mechanisms of renal (transcellular) Mg<sup>2+</sup> reabsorption in both lower vertebrates and mammals. The Impulsion Grant facilitated advanced training in specific techniques and approaches that allowed the elucidation of the physiologic relevance of new candidate genes that are postulated to play a role in renal Mg<sup>2+</sup> reabsorption. These techniques comprised:

- Methods to measure Mg<sup>2+</sup> reabsorption in the kidney of zebrafish (Figure 1B)
- Methods to measure electrolyte balance, namely of Ca<sup>2+</sup>, Na<sup>+</sup> and K<sup>+</sup>, in the zebrafish model
- Training in morpholino-knockdown approaches
- Validation of morpholino-knockdown approaches (out-of-target effects and specificity)

- Methods to (micro)dissect zebrafish larvae and study the pattern of gene expression of candidates in the pronephros (kidney in larvae)
- Methods to evaluate glomerular filtration rate and renal fluid flow in the zebrafish kidney
- Methods to extrapolate conclusions from the zebrafish model to human renal physiology
- Methods to evaluate the pathofunction of mutated genes in human genetic disease.

#### Identifying new genes that, when dysfunctional, lead to impaired renal Mg<sup>2+</sup> reabsorption

By applying the methodology developed in the previous key objective, the function of new candidates for renal Mg<sup>2+</sup> (transcellular) reabsorption in DCT was interrogated. Consequently, new players and molecular mechanisms controlling DCT Mg<sup>2+</sup> handling were identified. Therefore, the knowledge and models generated with the Impulsion Grant provide crucial and fundamental information for interventions that target renal Mg<sup>2+</sup> disorders by manipulating the gene / proteins involved in DCT Mg<sup>2+</sup> reabsorption. ■



**ROSER TORRA**  
Barcelona, Spain

## Moving toward a consensus on the management of Fabry disease

*The KDIGO Controversies Conference on Diagnosis and Management of Patients with Fabry Nephropathy (Dublin, October 2015)*

enzyme replacement therapy (ERT) and non-specific standards of care. Additionally, one of the most important aims of the conference was to identify knowledge gaps and deliver research recommendations.

The most controversial issue concerned ERT. There was agreement on the fact that ERT with recombinant human  $\alpha$ -galactosidase A (agalsidase) is the only currently available therapy aimed at the etiology of Fabry disease. However, agalsidase- $\alpha$  and agalsidase- $\beta$  have been studied in clinical trials with different primary endpoints and this hampers comparisons of their effectiveness. The evidence of efficacy of agalsidase is also incomplete due to the slowly progressive nature of Fabry disease and the relatively short trials with different clinical endpoints performed predominantly in (male) patients with classical disease. Nevertheless, based on ethical and feasibility considerations, it is very unlikely that further evidence from placebo-controlled trials will become available. Case series and post-marketing surveillance databases suggest that the earlier therapy is started, the better the outcome may be. This observation is in accordance with the hypothesis that glycolipid clearance is only effective before secondary, irreversible tissue injury has occurred.

There is no global agreement on when to start ERT, but in general development of signs or symptoms related to Fabry disease is an indication to start ERT in most countries. For the kidney, this means the development of chronic kidney disease (i.e. pathological albuminuria or decreased glomerular filtration rate [GFR]) or progressive decrease in GFR if ERT has not been started earlier for non-renal manifestations such as pain. Ideally, ERT should be started before clinical renal involvement, as this indicates that there is already established organ damage and fewer chances of great efficacy. Very early renal involvement (Fabry arteriopathy and segmental effacement of podocyte foot processes) has been identified in renal biopsies from patients with normal GFR and urinary albumin-to-creatinine ratio (UACR) <30 mg/g. Based on this finding, the benefits of early treatment before irreversible tissue injury occurs should be balanced against the burden of biweekly infusions in very young individuals. Stop criteria were met with some concern by patient organizations.

Overall, there is a suggestion that ERT is beneficial for kidney, cardiac and cerebral disease, especially when started

early in the course of the disease. In young patients there is some limited evidence of a dose-dependent clearance from podocytes over 5 years of follow-up. There is limited information on clearance in cardiac myocytes. Information on longer-term outcomes (5 to 10 years) is derived from non-controlled, single-center studies, follow-up of pivotal clinical trials or post-marketing data. ERT has no significant impact on established proteinuria but may reverse early albuminuria. Renal function is preserved in patients with a GFR >60 ml/min and controlled proteinuria after 5-10 years of ERT. In those with uncontrolled proteinuria or a reduced GFR (<60 ml/min), ERT alone does not seem to prevent further deterioration of renal function but may slow progression, though this remains to be demonstrated.

Although there are limited data, and only few comparative studies exist, it is suggested that dose of ERT may have an impact. However, the issue of dose has been muddled by the 5-fold difference in the label-recommended dose of the two available agalsidase preparations, and thus any discussion on dose must be interpreted in the context of the different enzyme preparations. In the absence of adequately powered, randomized controlled trials directly comparing 0.2 to 1.0 mg/kg/2 weeks, individual physicians should personalize decision making based on the weight they assign to the available placebo-controlled clinical trials, case-series and Canadian Fabry Disease Initiative, and clinical trial results.

There was a general agreement on the fact that Fabry disease patients should have access to coordinated care through expert designated centers, either through their local physician or by visiting such a center. This should apply equally to countries across the range of income. Regarding renal assessment, it was recommended to monitor albuminuria and GFR according to the KDIGO guidelines for CKD. It was suggested that a baseline renal biopsy may be helpful in assessing response to therapy of hard-to-clear cells such as podocytes.

Antibodies were also discussed. They develop in a substantial proportion of classical male patients with Fabry diseases and negatively influence the known biomarkers. Gb3 re-accumulation was noted in skin biopsies of patients with high antibody titers, and a recent study suggested more prominent disease progression in patients with circulating agalsidase inhibitory activity. However, there are *(continued on page 26)*

KDIGO (kidney disease: improving global outcomes) was established in 2003 as an independently incorporated, non-profit foundation governed by an international board. Its mission is to improve the care and outcomes of kidney disease patients worldwide through the development and implementation of global clinical practice guidelines. From 15 to 16 October, a group of experts met in Dublin, Ireland, at the KDIGO Controversies Conference on Diagnosis and Management of Patients with Fabry Nephropathy, chaired by Christoph Wanner and Raphael Schiffmann.

Fabry disease is an X-linked inborn error of glycosphingolipid catabolism resulting from deficient or absent activity of the lysosomal enzyme  $\alpha$ -galactosidase A. This enzymatic defect leads to the systemic accumulation of globotriaosylceramide and related glycosphingolipids in the plasma and cellular lysosomes of vessels, nerves, tissues, and organs throughout the body. The disorder is a systemic disease, manifesting as progressive renal failure, cardiac disease, cerebrovascular disease, small-fiber peripheral neuropathy and skin lesions, among other abnormalities. The conference aimed to address many concerns raised previously by the nephrology community, mainly related to screening and diagnosis,

## Session

**WGIKD/CME 8**

**Inherited Disorders:  
the kidney and  
beyond**

**TODAY, 09.00 – 12.15  
HALL N**

(continued from page 25) no clinical studies on the outcome of dose increases in patients with antibodies, or immunomodulation studies to reduce antibody titers in these individuals.

Turning to adjunctive therapy, it was highlighted that Fabry patients deserve to be treated with the same drugs as any patient with CKD regardless of their treatment with ERT. Specifically, the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) was deemed of utmost relevance. These drugs should be prescribed as soon as microalbuminuria appears, and the target would be proteinuria 300 to 500 mg/day or urinary protein-to-creatinine ratio (UPCR) < 0.5 g/g (50 mg/mmol). Because hypertension is not usually an issue in Fabry patients, lower proteinuria targets are usually associated with low blood pressure effects. Because albuminuria may appear very early during the course of the disease, it is extremely important to monitor it from the very early stages. Anticoagulation is recommended for use in paroxysmal atrial fibrillation. Recommendations for primary cardiovascular disease

prevention measures include: stop smoking, use statins and blood pressure control. There is no evidence to support the use of anticoagulants in Fabry patients with normal sinus rhythm. The use of acetylsalicylic acid is controversial for primary stroke prevention in patients without cardiovascular risk factors.

As mentioned above, one of the main purposes of the KDIGO Controversies meetings is to identify knowledge gaps and suggest recommendations for improvement. In that sense, there was agreement on the need to define when to start treatment in asymptomatic or paucisymptomatic patients, females and Fabry disease patients with non-classical disease. There is also a need for more information on the natural history of Fabry disease in classical female patients and non-classical Fabry disease patients, and the effects of ERT in these specific groups. Attendees raised their concern on the issue of antibodies. There is a need to develop standardized assessment techniques for neutralizing antibodies and for evaluating their impact on treatment individualization. If

a negative effect of antibodies on treatment responses is eventually confirmed, there then is a need to identify novel treatment strategies to overcome this effect. There is a definite need to know the very long-term outcomes of ERT and the impact of ERT in less-studied manifestations such as heart and central nervous system disease, valve abnormalities and aortic root dilatation, and lymphedema. It would be especially interesting to know the very long-term outcomes for those patients who started ERT when asymptomatic or paucisymptomatic. Knowledge on criteria and biomarkers for dose individualization would improve ERT prescription and outcomes, and also would facilitate the definition of therapeutic failure. At the same time, it may clarify whether progression of Fabry disease while on ERT indicates therapeutic failure. Finally, attendees encouraged the collection of biobank biological samples from Fabry Disease patients for use in future research. The manuscript on the KDIGO Controversies Conference on Diagnosis and Management of Patients with Fabry Nephropathy will be published shortly in *Kidney International*. ■



**KITTY JAGER**  
Amsterdam, The Netherlands

## New Results from the ERA-EDTA Registry

Pippias et al. showed a declining RRT incidence, particularly in patients aged 45-64 years, 65-74 years and secondary to diabetic nephropathy. In addition, the adjusted RRT patient survival continued to improve. "My conclusion is that the efforts of the nephrology community may finally pay off. Eventually, prevention may have started to work", comments Professor Kitty Jager.

### CKD prevalence varies a lot across European countries and regions

So far, it has been estimated that about 10% of the population in Europe is affected by chronic kidney disease (CKD). The working group coordinated by Katharina Brück from the Academic Medical Center in Amsterdam performed an analysis of 19 general population studies from 13 different European countries [1]. The results revealed a great heterogeneity across Europe: The prevalence of CKD, stage 1-5 varied between 3.31% in Norway and 17.3% in northeast Germany. Even if only the more severe stages of CKD were taken into account (CKD 3-5), the difference still remained substantial: The prevalence of these later stages was only 1.0% in central Italy, but 5.9% in northeast Germany. "It was quite surprising for us to learn the great variation in CKD prevalence across European countries and regions", explains Prof. Kitty Jager, epidemiologist and managing director of the ERA-EDTA Registry. But how can these differences in CKD prevalence among European countries be explained? "To be honest, this is a question we cannot answer yet. We know from this study that the difference in prevalence of CKD is largely independent of the prevalence of diabetes, hypertension, and obesity", explains Professor Kitty Jager. "There are many other factors that might contribute to it, e.g. human and environmental factors, genetic factors, the impact of public health policies on disease prevention and early detection – which vary a lot across Europe –, but the differences might also be due to heterogeneity of included studies with regard to laboratory methods and sample selection". As Professor Ziad Massy, Paris, chairman of the ERA-EDTA Registry, points out, further epidemiological research would be necessary: "We know that CKD prevalence varies a lot across Europe, but obviously beyond traditional risk factors, other factors – either related to the patient or the environment – need to be determined. Therefore the work of the ERA-EDTA Registry is immensely important – we have to work actively to find out what puts us at risk of CKD."

### Declining RRT incidence in Europe

Another study, which also analyzed data from the ERA-EDTA Registry and was published in *NDT* [2], brought encouraging news for European nephrology: This study by Maria

### Patients with scleroderma might benefit from transplantation

Zdenka Hruskova and colleagues performed a study [3] among patients on renal replacement therapy (RRT) due to systemic sclerosis (scleroderma), a rare multi-system autoimmune disorder characterized by immune activation, vasculopathy and excessive collagen deposition. The study aimed to determine the incidence and prevalence of end-stage renal disease due to scleroderma in Europe and to describe patient characteristics, renal recovery, and survival rates of patients with scleroderma on RRT. Using data from the ERA-EDTA Registry, a total of 342 patients with scleroderma were included. They comprised 0.15% of 234,954 patients who started RRT between 2002 and 2013. Characteristics and outcomes of patients with scleroderma were compared to age- and sex-matched control groups of patients with diabetes mellitus and non-scleroderma-non-diabetic patients. The study confirmed that patients with scleroderma had a higher renal recovery rate than the other patients, but the results also showed that survival on RRT in patients with scleroderma was worse than in all other diagnoses, including patients with diabetes mellitus. Another major finding was that patients with scleroderma who received a kidney transplant showed favourable survival outcomes. This, of course, has an implication for clinical practice – supporting the use of kidney transplantation in these patients.

### What is the lifetime risk of RRT for kidney donors? Find out in the ERA-EDTA registry symposium tomorrow!

Jan van den Brand et al. have been working on a study on lifetime risk of renal replacement therapy (RRT) for end-stage renal disease. This publication will be relevant for potential living kidney donors to assess the average lifetime risk of RRT given their age and sex. **The results of this study will be presented tomorrow!** ■

### References

1. Brück K et al. *JASN* 2015 Dec 23 [Epub ahead of print]
2. Pippias M et al. *NDT* 2015 Sep 11 [Epub ahead of print]
3. Hruskova Z et al. in progress

## ERA-EDTA Registry

### Session

**ERA-EDTA REGISTRY / CME 20**  
**Crosstalk in renal epidemiology**

**TODAY, 15.30 – 17.30**  
**HALL M**

**SYMPOSIUM 3**  
**ERA-EDTA Registry**

**SUNDAY, 08.00 – 09.30**  
**HALL E**

### Imprint



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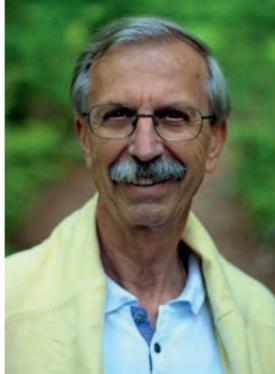
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**When to use CNIs in membranous nephropathy**

**MANUEL PRAGA**  
Madrid, Spain


**Preoperative assessment of vascular capital for a new access**

**PEDRO PONCE**  
Lisbon, Portugal


**Predictors of fistula function**

**MARKO MALOVRH**  
Ljubljana, Slovenia


**Markers of frailty: myostatin**

**THOMAS BERND DSCHIETZIG**  
Berlin, Germany


**Non-pharmaceutical and pharmaceutical strategies to enhance fistula maturation and primary patency**

**JAN H.M. TORDOIR**  
Maastricht, The Netherlands

## Tomorrow's Highlights

**Plenary Lecture 1**

10.45 – 11.30, HALL A

**A network-oriented view of living systems to complement the reductionist** – Andrew Kasarskis, New York, U.S.A

**Late Breaking Clinical Trials**

11.45 – 13.15, HALL A

**The Lancet/The Lancet Diabetes and Endocrinology Symposium**

15.15 – 16.45, HALL D

**ASN Highlights**

15.15 – 16.45, HALL A

**ERA-EDTA & ESC Joint Symposium**

17.00 – 18.30, HALL A

Welcome address  
**Gert Mayer**, Congress President

Presidential address  
**Andrzej Więcek**, ERA-EDTA President

Presentation of the ERA-EDTA Award for Outstanding Educational Contributions to Nephrology to **Rosanna Coppo**

Presentation of the ERA-EDTA Award for Outstanding Basic Science Contributions to Nephrology to **Pierre Ronco**

Presentation of the ERA-EDTA Award for Outstanding Clinical Contributions to Nephrology to **Christoph Wanner**

Presentation of the Award for Outstanding Contributions to ERA-EDTA to **Raymond Vanholder**

Presentation of the Stanley Shaldon Award for Young Investigators to **Emilie Cornec-Le Gall**

Presentation of the ERA-EDTA Honorary Membership to **J. Douglas Briggs**

Announcement of collaboration among ASN, ERA-EDTA and ISN

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## Writing a suitable PD prescription in 2016

*How to individualize peritoneal dialysis to meet each patient's needs*

Peritoneal dialysis (PD) has long been established as a mode of treatment for end-stage renal disease (ESRD) patients. Although used in smaller numbers in comparison to its bigger sister hemodialysis (HD), PD has proved effective, assuring acceptable survival and good quality of life. Moreover, in the last 10-15 years, outcomes have improved, new solutions have been introduced, prescriptions have been individualized, and the method offered in various clinical settings and situations. The basic prescription for continuous ambulatory PD (CAPD) and automated PD (APD) has evolved to more specifically meet the needs of certain groups of patients and peritoneal membrane transport characteristics. Among the main advantages of PD as a chronic therapy is a fact that treatment is performed in the home environment and that it allows for flexibility of the therapy.

### PD for young and elderly

PD therapy is a good option for young patients in whom dialysis treatment may be incorporated into their lifestyle, school and work. Although APD appears to be a preferable method that allows for daytime freedom, CAPD with its independence from the machine may also be an option. As increasing numbers of elderly patients enter dialysis treatment, PD offers a hemodynamically stable treatment that does not require frequent visits to hospital. Modern connections provide patients with simple and safe ways of performing dialysis procedures. The therapy can be planned and introduced slowly, with treatment schedules individualized in number and volume of exchanges. In the end-of-life of care, where alleviating symptoms rather than prolonging survival is an issue, the number and volume of exchanges may be reduced and 'days off' accepted. Both CAPD and APD may be performed by a helper as in assisted PD. In many countries, a system of assisting nurses provide support at the patient's home or the nursing home; in other countries family members can be educated in dialysis procedures. New technologies using telemedicine are at the doorstep and will result in substantial progress in patient management, providing online help and confidence, and reducing barriers to home therapy among the elderly population.

### PD for AKI and in the unplanned setting

While developed countries mainly use hemodialysis for treating acute kidney injury (AKI), PD has been increasing-

ly utilized in developing countries, mainly due to its cost effectiveness and minimal infrastructure requirements. The International Society of Peritoneal Dialysis has published guidelines on the use of PD in AKI and, according to patient requirements and facility options, the therapy can be performed as intermittent, continuous-flow, tidal and high-volume PD. These different techniques deliver urea clearance from 8 up to 35 ml/min, and PD solutions with bicarbonate as the buffer are recommended due to the risk of lactate accumulation and worsening of metabolic acidosis. In addition, it has been shown that late-referred patients may start PD in an unplanned setting, with a lower risk of serious complications than that associated with unplanned start on HD with a temporary central venous catheter.

### PD for fast and slow transporters

Assessment of peritoneal membrane characteristics is fundamental to PD prescription. Patients with average transport usually do well on both CAPD and APD with adequate volumes and times of exchanges. The challenge of obtaining adequate treatment in terms of small-solute clearances and hydration status concerns patients with marginal transport characteristics. Overhydration, cardiovascular complications, malnutrition and in consequence higher mortality and technique failure have been shown in fast transporters, but this negative effect can be abolished by the appropriate APD regime. On the other hand, slow transporters on APD may be hypertensive due to inadequately short night cycles and negative sodium balance. These patients may be more adequately dialyzed with CAPD or if their preference is to stay on APD, with continuous cyclic PD (CCPD) involving fewer cycles at night and an obligatory 'wet' day with or without additional exchanges performed by cycler. Since membrane characteristics change with time on dialysis, the evaluation of transport should be performed routinely at least once a year to guide the PD prescription and further individualize the treatment.

### PD for diabetics

ESRD in type 2 diabetes has been called a medical catastrophe of worldwide dimensions and around 50% of patients on PD are diabetics. As stated in the recent Clinical Practice Guidelines on the management of patient with diabetes and chronic kidney disease, there is no superiority of HD over PD and vice versa. These patients pose a challenge, in that they are more prone to atherosclerotic and inflammatory complications. In addition, glucose-based solutions may cause problems in controlling glycemia and obesity, and with time and the appearance of vascular complications these patients may lose their independence and capacity to perform PD procedures. Low-glucose re-

gimes, and supported and assisted PD may be useful in this group of patients.

### PD for cardiorenal syndrome (CRS)

Heart failure is the most common reason for hospital admission in patients older than 65. In the chronic setting, where patients present with various degrees of heart failure and slowly declining renal function, PD appears to be a therapy with the ability of simultaneously addressing both organs. It has been shown to provide efficient ultrafiltration and sodium extraction in volume-overloaded patients, while correcting the metabolic consequences of diminishing glomerular filtration rate. Again, the flexibility of PD means that the number, volume and osmotic agent of exchanges can be easily adjusted. The treatment is usually started with one exchange daily with glucose or preferably glucose polymer solution to provide ultrafiltration, and later can be augmented according to declining renal function.

### Biocompatible solutions and icodextrin

New biocompatible solutions offer biochemical and metabolic benefit and may prolong longevity of the peritoneal membrane, technique and patient survival. There are solutions with low glucose degradation product (GDP) concentration, with bicarbonate as a buffer instead of lactate, and as long as the cost is not prohibitive, they should become routine in 2016. Polyglucose and aminoacid solutions may be used as low-glucose regimens, preserving the peritoneal membrane and offering benefit for the metabolic profile.

### Adequacy and hydration

Adequacy values in small solute clearances have not changed for the last 10 years. We should aim for  $Kt/V$  of  $\geq 1.7$ , with attention paid to creatinine clearance in patients on APD. Volume status should be closely monitored and bioimpedance spectroscopy appears to provide objective measurement for overhydration. As over 50% of PD patients are currently on APD, adapted APD may be considered an option with high-volume, longer-time cycles to obtain optimal solute clearance and shorter and lower volume exchanges to achieve adequate ultrafiltration. Variable calcium concentration is another possibility to individualize treatment, with around 80% of patients requiring Ca concentration of 1.25mmol/l.

In conclusion, in 2016 PD can be offered to different populations in various clinical settings. With better solutions and more appropriate, individualized regimens, ESRD, AKI and CRS patients may benefit from this form of therapy. ■

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# When to use CNIs in membranous nephropathy

*Useful therapeutic agents, but they have important drawbacks*

Calcineurin inhibitors (CNI), both ciclosporin and tacrolimus, are well known to nephrologists, given key role of these drugs in the immunosuppression of kidney transplant patients. But they are also widely used in the treatment of various glomerular diseases, including membranous nephropathy (NM).

The KDIGO guideline for the treatment of glomerular diseases recommends CNI as an alternative to classic treatment of NM based on the modified Ponticelli regimen (alternating monthly cycles of corticosteroids and cyclophosphamide). This recommendation is based on the favorable results of prospective randomized controlled trials (RCT) that compared CNI with control groups. In one study, published in 2001, Cattran et al [1] randomized 51 patients to ciclosporin plus prednisone versus placebo plus prednisone for 26 weeks; 75% of the patients allocated to ciclosporin reached remission (partial in most cases) of nephrotic syndrome, versus 22% in the placebo group. The initial dose of ciclosporin was 3.5 mg/kg/day, then adjusted to maintain blood levels between 125 and 225 mg/L. Ciclosporin tolerance was good and there were no differences in renal function, although a higher proportion of patients treated with ciclosporin developed hypertension. However, the proportion of patients in whom nephrotic syndrome recurred after ciclosporin discontinuation was high at 43%.

In 2007, Praga et al [2] published the results of an RCT comparing tacrolimus monotherapy (without corticosteroids) versus supportive therapy in 48 patients with NM. The initial dose of tacrolimus was 0.05 mg/kg/day, subsequently adjusted to maintain blood levels around 4 ng/ml. Treatment was maintained for 6 months at full doses, followed by 6 months of tapering. Like ciclosporin, tacrolimus was very effective in inducing remission (mostly partial) of nephrotic syndrome: 82% versus 24% in the control group. In addition, a greater proportion of patients in the control group exhibited declining renal function, demonstrating that remission of proteinuria, even partial, exerts a significant renoprotective influence in NM. Tacrolimus was well tolerated, with a few minor side effects but, as with ciclosporin, a high percentage of patients (47%) relapsed during tacrolimus tapering or after its withdrawal.

A recently published Spanish collaborative study [3] reported the results of MN treatment with tacrolimus in the real-life daily clinical practice. It collected 122 MN patients who had been treated with tacrolimus. Mean duration of treatment was 17 months, including a full-dose and a taper-

ing period, and the percentage of remission was 60%, 78% and 84% after 6, 12 and 18 months of treatment, respectively. Notably, the amount of proteinuria at baseline significantly predicted remission: the lower the baseline proteinuria, the higher the probability of remission. Most of the patients (92%) had received tacrolimus monotherapy, with no corticosteroids. Among responders, 42% achieved complete remission and 58% partial remission of the nephrotic syndrome. Almost half (44%) of the responder patients relapsed. The amount of proteinuria at the onset of tacrolimus tapering was significantly higher in relapsing patients. By multivariable analysis, the presence of a partial remission versus complete remission at the onset of tacrolimus tapering and a shorter duration of the tapering period significantly predicted relapses.

The favorable influence of CNI in MN has been largely attributed to the non-specific antiproteinuric effect of these drugs, based on their effects on podocyte cytoskeleton. It must be stressed, however, that CNI are also potent immunosuppressive drugs and that their beneficial influence in MN patients are likely mediated by their immunosuppressive properties. In fact, several studies have reported a clear and sustained decrease or disappearance of antibodies against M-type phospholipase A2 receptor (PLA2R) in patients with MN treated with tacrolimus.

Therefore, CNI are effective agents for MN treatment. However, it should be underlined that their use presents clear advantages but also remarkable drawbacks in this setting. On one hand, one of the main advantages of CNI is good tolerability, with few and minor side effects in skilled hands. Another advantage is their remarkable efficacy, most patients (between 75-85%) achieving remission of nephrotic syndrome within few months of treatment.

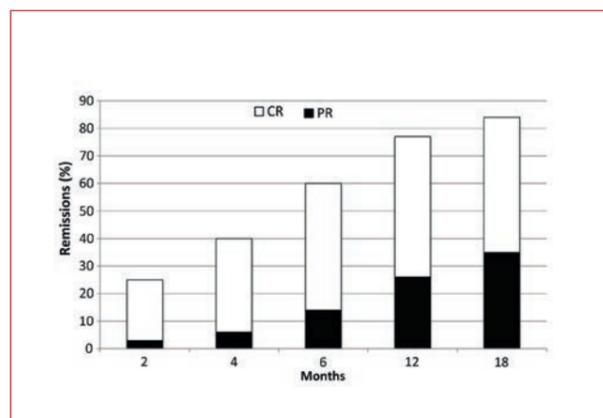
By contrast, CNI also have clear disadvantages. As shown in the aforementioned Spanish observational study, the response to treatment is significantly determined by the amount of initial proteinuria, being more resistant those cases with greater degrees of proteinuria. Furthermore, CNI are difficult to manage in patients with established impairment of renal function or with declining renal function, since they can by themselves induce renal impairment, either by an acute, reversible vasoconstriction at the onset of treatment, or by a progressive and in some cases irreversible nephrotoxicity in the long term.

Therefore, the profile of CNI does not seem the most appropriate for the treatment of aggressive types of NM, with massive proteinuria and/or declining renal function. These patients, which in our experience account for 20-25% of cases, should probably be treated with drugs other than CNI, as in Ponticelli's regimen or with rituximab. In an important RCT [4] conducted in the United Kingdom and published in 2013, 108 patients with nephrotic syndrome and declining

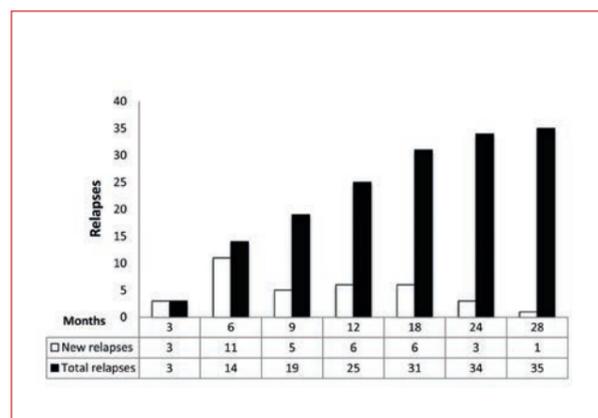
renal function (a glomerular filtration rate decrease >20% in a 2-year period before the study) were randomized to treatment with prednisone + chlorambucil, ciclosporin, or supportive treatment alone. The primary outcome was a further 20% decline in renal function. Those patients treated with alternating monthly cycles of prednisone and chlorambucil for 6 months had a significantly lower risk of further renal function decline than those allocated to ciclosporin or supportive treatment, and there were no differences between the latter. The authors concluded that ciclosporin should be avoided in MN patients with declining renal function.

The other major disadvantage of CNI is the high rate of nephrotic syndrome relapse after their discontinuation. As shown by the Spanish observational study, the higher the residual proteinuria at the onset of CNI tapering, the greater the risk of relapse, which in turn can be minimized by a longer tapering period. Alternatively, some observational studies suggest that rituximab, when administered just before the onset of CNI tapering, can reduce the risk of relapse. Rituximab has proven to be effective in decreasing the risk of relapse in other types of nephrotic syndrome (for instance in corticoid-dependent minimal change disease) and, according to these preliminary data, it could also be effective in this setting.

It seems clear that CNI are useful therapeutic agents in NM, but probably a particular subset of patients without massive proteinuria and with stable renal function should be selected to receive these drugs as initial therapy. Prospective studies are needed to confirm these data. In this regard, the ongoing STARMEN (which compares tacrolimus + rituximab versus the modified Ponticelli regimen) and MENTOR (comparing rituximab versus ciclosporin) trials will certainly provide decisive results to better define the profile of patients eligible for CNI treatment in MN. ■



**Figure 1: Percentage of complete (black) and partial (white) remissions after the onset of tacrolimus treatment.** © Praga



**Figure 2: Monthly incidence and cumulative number of relapses after the onset of tacrolimus tapering.** © Praga

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## Markers of frailty: myostatin

*A key player in cachexia and wasting states*

In 1997, McPherron and Lee created the so-called Mighty Mouse. Owing to the knockout of a new member of the TGF- $\beta$  superfamily of peptides, this mouse line was extremely hypermuscular and also characterized by very low body fat. The new peptide, a powerful negative muscle regulator, was named myostatin. The discovery of myostatin elucidated several naturally occurring 'double-muscling' phenotypes of great agricultural interest; for example, the Piedmontese, Asturiana, Marchigiana, and Belgian Blue cattle breeds.

Since then, this outstanding discovery has ignited enormous scientific and economic interest for obvious reasons. In man, the development of myostatin-inactivating therapies holds great promise to patients suffering from cachexia, muscle dystrophy, or trauma. At the same time, gene therapy that knocks down myostatin is clearly alluring to professional athletes seeking to break the natural limits of human physiology. Moreover, myostatin has recently been reported to be significantly involved in different cardiovascular and metabolic pathologies, such as heart failure, insulin resistance, and cachexia.

Myostatin, also known as growth differentiation factor-8 (GDF-8), belongs to the TGF- $\beta$  protein family and consists, in its full-length prepro-myostatin form, of 375 amino acids in humans. Prepro-myostatin is composed of an N-terminal signal peptide (23 aa, theoretical molecular weight 2.6 kDa) followed by the pro-peptide domain (aa 24-266, 27.7 kDa) and the C-terminal mature domain (aa 267-375, 12.4 kDa). The myostatin peptide is remarkably conserved among species. In the N-terminal pro-peptide, the mouse shows 96% and 99% homology to the human and the rat, respectively; the sequence of the mature C-terminal myostatin is completely conserved. Myostatin is expressed in skeletal muscle and, to a lesser extent, in adipose tissue and also in cardiomyocytes. Inflammatory cytokines, glucocorticoids, insulin-like growth factor-1, angiotensin-II, urotensin-II, and urocortin are among the most important upregulators of this peptide.

Different inhibitors and enzymes control secretion, posttranslational processing and receptor binding of myostatin, which constitute a complex and highly dynamic network with multiple regulation sites. Proteolytic processing yields the dimerized C-terminal mature domain, which is kept inactive by being non-covalently bound to the latency-associated peptide (LAP, i.e. the N-terminal pro-domain) and additional inhibitors (follistatin, follistatin-related peptide, growth/differentiation factor-associated serum protein [GASP]-1, and GASP-2), and prevented from receptor binding. Latent myostatin appears to be the major circulating form of the peptide. It is set free to bind its receptor by members of the bone morphogenetic protein-1/tolloid (BMP-1/TLD) family of metalloproteases. Myostatin interacts with a hetero-tetrameric receptor composed of activin receptor IIB and ALK4/5 dimers.

Myostatin's inhibitory effect on insulin sensitivity can be attributed prevalently to its negative impact on metabolically active lean muscle mass. In myocardium, myostatin promotes fibrosis, counteracts hypertrophy and is moderately upregulated in chronic systolic heart failure. In heart failure, as well as in several other chronic pathologies (for example, chronic kidney disease [CKD], chronic pulmonary disease, cancer, and chronic inflammation), myostatin plays a pivotal role in inducing cachexia.

Cachexia is defined as a complex metabolic syndrome characterized by weight loss due to chronic disease that exceeds 5% of body weight and may cause loss of tissue from 3 compartments: lean tissue, fat, and bones. It is associated with significantly increased mortality. The term 'cachexia' has to be distinguished from 'muscle wasting', which denotes loss of skeletal muscle in the absence of weight loss; 'sarcopenia', in turn, is defined as wasting in the course of aging. Cachexia is initiated and sustained by a severe dysbalance that favors catabolic pathways. The major proteolytic pathways—i.e. the ubiquitin-proteasome system, the lysosomal system (cathepsin L and others), the calcium-dependent system (the calpain proteases family), and the caspase-dependent apoptosis system—are chronically stimulated by a multitude of disease-related factors. These include inflammatory cytokines (TNF- $\alpha$ , interleukin-1 and -6, interferon- $\gamma$ ), angiotensin-II, glucocorticoids, melanocortin, as well as reactive oxygen and nitrogen species. The main counter-players, though diminished, outweighed or overridden in the course of disease, are physical activity, the growth hormone-IGF-1-ghrelin axis, insulin, and the anabolic steroids.

Myostatin executes its deleterious effects via the following pathways, which have also been found to be active in CKD-related cachexia. First, myostatin, via its Smad pathway or via suppression of Wnt4/ $\beta$ -catenin signaling, inhibits the transcriptional factors myf5, myoD and myogenin, which are essential for myogenesis and myocyte repair. Second, the MEK-1-ERK-1/2 cascade plays a role in differentiation suppression by myostatin. However, the PI3K-Akt pathway poses the potentially most relevant crossing point, receiving input from both myostatin and its counter-players, particularly IGF-1. Akt phosphorylates, and thereby inactivates the FoxO transcription factors that are crucially involved in igniting protein degradation by the ubiquitin-proteasome system. Since myostatin inhibits Akt activation, it favors protein catabolism. Akt also inactivates GSK-3 $\beta$ , which promotes degradation of cyclin D1—Akt inhibition by myostatin serves to decrease cyclin D1 and inhibit cell proliferation in the G1 phase. Eventually, the Akt-mTOR-p70 S6K axis switches protein synthesis on and is similarly blocked by myostatin. Accordingly, ActRIIB antagonism and/or inhibitory myostatin antibodies have emerged as promising therapeutic tools to treat the cachexia syndrome. Phase II studies with promising results have already been conducted, and the approach will doubtlessly be pursued further in the near future.

Consequently, the issue of myostatin as a biomarker for cachexia has drawn broad attention. Currently, there are commercially available ELISA kits, and mass spectrometry-based methods are being developed for routine clinical practice. Though its pathophysiologic involvement in renal cachexia is established, the few data available on circulating myostatin in CKD patients that appear to indicate a myostatin increase with disease progression. However, the diagnostic performance of current myostatin methodology to identify cachexia and/or wasting is only moderate. This may be attributable to the regulation of myostatin bioactivity by different inhibitors, the complexity of which escapes simple measurements of circulating levels, or the fact that there is overlapping short- and long-term regulation of myostatin.

In conclusion, the negative muscle regulator myostatin is a key player in cachexia and wasting states. Therapeutic approaches towards myostatin inhibition are currently being tested in clinical studies. The biomarker myostatin is interesting, but needs further critical evaluation that might result in new diagnostic concepts. ■

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## Preoperative assessment of vascular capital for a new access

Vascular Access (VA), the Achilles heel of the dialysis patient, is a major cause of dialysis morbidity, accounting for up to 25% of all hospital admissions and 60% of all dialysis programme costs in the first year in the US. Native AV fistulas (AVF) implanted prior to the need for dialysis are considered to be the best VA for most incident and prevalent patients, and are clearly the less expensive option in the long term.

However, due to an high nonmaturation rate [1], designing the care process to maximize the number and maturation of AVFs includes: early nephrology referral; early VA education of patients and hospital staff; avoiding peripheral and CVC lines; timely surgical referral; choice of an upper arm AVF for those at risk of failure; having the right surgical expertise; preferably operating in a Vascular Access Centre; and last but not least, the topic of this presentation, preoperative mapping of vascular capital. Vascular mapping includes any technique that produces information on the patient's inflow and outflow anatomy as it relates to arteriovenous access creation. It can be performed by history and physical examination (PE); Doppler ultrasound evaluation (DUS); or angiographic mapping (AM).

According to the recommendations of NKF-KDOQI Clinical Practice Guidelines for Vascular Access [2], evaluations carried out before placement of a permanent haemodialysis VA should include: history and physical examination (level B), duplex ultrasound of the upper-extremity arteries and veins (level B) and central vein evaluation in the case of a previous catheter or pacemaker (level A). This assessment would preferably be performed by the surgeon who will create the vascular access.

History and physical examination should assess risk factors for worst outcomes, such as female gender, black race, age older than 85 years, diabetes, peripheral vascular disease, or congestive heart failure. It is also essential crucial to trace the history of previous central catheters, the presence of cardiac rhythm devices, and to look for swelling of arm, breast, facial and collateral veins. The next step should be vein inspection following tourniquet placement to determine diameter, length of potential cannulation segment, tortuosity and distance from the surface. Blood pres-

sure must also be measured, looking for pulse asymmetry, and a modified Allen test must also be conducted, using a pulse oximeter, to assess the patency of the palmar arch. Inaccuracies can be expected when conducting physical examinations of obese patients, diabetics, or the elderly.

Venography mapping is usually performed by injection of a radiocontrast agent in a peripheral vein in the dorsum of the hand. For a better assessment of future inflow, we can also cannulate the brachial artery. In general, we use 10 to 20ml of a low osmolar contrast agent, diluted 1:1 in normal saline, with image acquisition of 15 frames/sec. We define vessel suitability as: a) vein diameter >2.5mm, b) straight cannulation segment >8cm long, c) continuity with central veins, d) no stenosis. There are no good comparative studies with ultrasound, but in a retrospective study, venography had higher AVF rates (51.3%) than US (34%) [3].

Venography provides better visualisation of central veins, mainly in obese patients, but it is more expensive, occupies the angiography suite with a non-interventional diagnostic test, does not address fibrosis, distensibility or blood flow of the vessel wall and it is not always easy to cannulate a suitable vein in the hand. The risk of contrast-induced nephropathy in pre-dialysis patients (CKD 4/5) with doses of <20ml was less than 0 to 4% and always reversible [4, 5].

Doppler ultrasound, on the other hand, can deliver a morphologic and haemodynamic evaluation, uniformly predict status and availability of vessels for VA creation, is harmless, low-cost, can be performed at the bedside in the dialysis unit, but is suboptimal for assessing central vessels. The Doppler ultrasound vascular mapping procedure includes: A) a morphological (B-) mode providing anatomical evaluation on the basis of vessel diameter, wall thickness, wall alterations (calcification), steno-obstructive lesions, anatomy variations, and B) a haemodynamic (colour and Doppler) mode providing functional evaluation on the basis of peak systolic velocity, blood flow and resistance index. Intuitively and for many authors, preoperative mapping results in a marked increase in AVF placement and a reduction in the use of catheters [6, 7, 8]. Comparing preoperative US Doppler with P.E., a dramatic 64% vs 34% increase in AVF creation was found (Allon. KI 2001, 60:2013), as well as a reduction in graft placement from 62% to 30% and in tunnelled catheter insertion from 24% to 7% [6].

In another study in which Ilhan and coworkers [9] compared 63 patients evaluated with PE + DUS vs 76 with PE only, demonstrated that constructed AVF increased significant-

ly from 75% to 97% (P=.001) with preoperative ultrasonographic vascular mapping, and that the patency rate after 6 months was 80.7% for the PE group and 93.4% for the PE+DUS.

However, a systematic review of 3 RCTs examining the effect of DUS on fistula formation showed a modest, statistically insignificant increase in maturation among those receiving mapping compared with physical examination alone, no evidence of an increase in the proportion of fistulas ultimately used for dialysis, or a reduction in catheter use. Furthermore, the number of procedures required to maintain access function increased (S. D. Kosa et al., unpublished data). Apparently, vascular mapping mainly influences the type or location of the VA in younger and less experienced surgeons [10, 11], and we must not forget that success does not correlate with vessel diameter but with flow, mainly the day after the procedure [12].

In conclusion: preoperative physical examination provides essential information on patients needing AVF construction, but is rarely sufficient nowadays because an increasing proportion of HD patients have a compromised vasculature as a result of age, diabetes, many years of dialysis therapy, and prior HD catheters. Noninvasive assessment by duplex sonography, at least in selected patients with a higher risk of VA failure, is very helpful in locating veins that are not clinically visible and also provides information about the functional characteristics of veins, including venous outflow. Minimum diameters, velocities and haemodynamic behaviour of veins and arteries have been associated with an increased chance of maturation of a fistula.

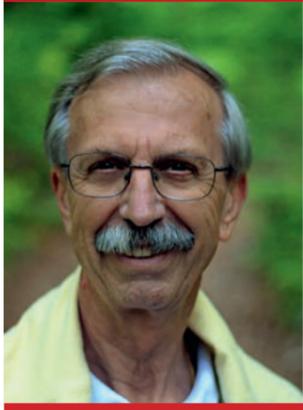
Duplex sonography is also the method of choice for evaluation of arteries. A calcified artery with a small lumen and thickened wall will never provide adequate fistula function. ■

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## Predictors of fistula function

should not be a limiting factor when deciding which patients should have which vascular access. Those differences can be related to a different population, or confounding factors that may have influenced the maturation process.

Female gender has been associated with increased risk of AVF non-maturation in several studies. The reason for this remains unclear. Historically, the higher risk of AVF failure in females was attributed to smaller blood vessel diameter compared to males. However, despite female blood vessels being smaller in calibre than the equivalents in males, arterial diameters in females have been shown to be larger than the recommended minimum diameter of 2.0 mm with similar venous diameters.

Diabetes was identified as a risk factor associated with primary functional patency loss. The results of some studies indicate that patients with diabetes may encounter more complications during fistula life, but, if treated adequately, functionality can be maintained as long as in patients without diabetes, regardless of the anatomic location of the anastomosis. The clinical evaluation and decision-making process regarding vascular access should be identical in diabetic and non-diabetic patients.

In some studies, certain factors were found to influence maturation of AVF, such as previous kidney transplant, platelet count of less than 100 109/L, and low haemoglobin levels. The maturation rate was also higher in patients who had AVFs created before the start of HD. Other studies showed that the primary patency rate was higher in HD patients in comparison with non-dialysis patients. The mechanism by which HD affects AVF patency is not known, but it seems that a role is played by haemostasis and blood flow changes in the HD patient. Some authors found that maturation of proximal AVFs was much greater than that of distal AVFs.

AVF failure is often attributed to vascular co-morbidity. Physical examination has traditionally been used to identify a suitable artery and vein for AVF formation. Vessels are considered suitable if the artery has a good pulse, and the vein is patent and of good calibre.

Preoperative evaluation with ultrasound may select suitable vessels and reduce AVF failures, especially in elderly patients, patients with diabetes and vascular disease, and should be used routinely to evaluate all patients prior to creation because of the good correlation between preoperative determi-

nation and perioperative findings. Good patency rates were obtained in patients with AVFs that were created on the basis of vein selection: diameter of cephalic vein at the wrist  $\geq$  2-2.5 mm or upper arm veins  $\geq$  3 mm. The ability of the vein to increase the diameter at inflated cuff (distensibility) for 0.4 mm or  $>$  15% is another predictor for AVF function. Vein distensibility (VD) is a predictor of AVF success. Measurement of VD may be helpful in choosing the most suitable access type for each individual patient, possibly improving access patency.

The suitability of the artery for AVF creation is determined by its diameter, wall morphology and hyperaemic response. Preoperative internal diameter in the feeding artery is crucial, and most of the literature data suggest diameters of 2.0–2.5 mm. A resistance index of  $<$  0.7, or even a change from high-resistance flow to low-resistance flow in the potential feeding artery after opening of the fist (hyperaemic response), indicates that arterial blood inflow will increase sufficiently so that the chance of successful creation of an AVF will exist. Increased intima-media thickness and severe calcifications predict AVF failure with high probability.

Factors associated with AVF failure to mature are likely to vary from population to population. It is important to investigate local rates of AVF failure to mature and associated predictors of AVF patency in order to guide appropriate vascular access decision-making. The failure rate of autogenous AVFs which fail to mature covers a wide range and differs from centre to centre. In that regard, numerous studies have been performed in an attempt to correlate the factors responsible for failure of maturation of autogenous AVFs. Information obtained from further studies should facilitate the creation of regionally applicable predictive models encompassing a combination of clinical and ultrasound parameters to help stratify patients into relevant categories of risk for AVF failure.

Given the abundance of studies and the considerable diversity in results on the importance of the various factors that could affect the functioning of the AVF, it is necessary to process each individual patient and to adjust the results of that patient. ■

A mature and functional arteriovenous fistula (AVF) is considered the best modality for haemodialysis (HD) access when compared to arteriovenous grafts (AVG) and central venous catheters (CVC). However, it is expected that approximately one third (20%–50%) of AVFs will fail to mature into useful access. Although the chances of an AVF failing are high, they should still be considered as the first option for any patients planned to start HD sessions, and for those who have already started HD. For a fistula to mature, there must be sufficient delivery of intra-access blood flow and pressure, which is dependent on adequate cardiac output (systemic blood pressure) and a feeding arterial vessel of good quality that will be able to transmit this high pressure to an accepting, unrestricted (i.e. no anastomotic stenosis), compliant, and distensible outflow venous vessel.

There is conflicting evidence about the impact of various demographic characteristics of patients on the functional maturation of native AVFs. A variety of patient demographics such as age, gender and cause of end-stage renal disease, access characteristics such as site or vessel morphology, and patterns of practice such as timing referral and placement have been associated with nonspecific fistula use, adequacy and failure. Published studies that have evaluated predictors of successful fistula have varied in their study endpoints and definitions, study design and size, patient population, and clinical considerations. These discrepancies make it difficult for a clinician to determine the relative importance of these potential risk factors and to determine which clinical variables to apply in assessing the likelihood of achieving a mature fistula in patients referred for a permanent access.

Age was thought to be associated with AVF maturation. Elderly patients ( $>$ 65 years) are traditionally thought to have worse patency rates and to be more likely to suffer from AVF non-maturation (Rodríguez 2000, Peterson 2008). However, this has been disputed by other authors (Lok 2005, Persic 2009, Renaud 2012, Baschar 2015). It was argued that age

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## Non-pharmaceutical and pharmaceutical strategies to enhance fistula maturation and primary patency

The vascular access is the lifeline for the haemodialysis (HD) patient. Autologous arteriovenous fistulae (AVF) are considered to be the first and best option for HD access and more favourable compared to the use of arteriovenous grafts (AVG) and central venous catheters (CVC). The major drawback of creating an AVF is the high failure-to-mature (FTM) risk, which ranges from 30 to 50% of all newly-created AVFs. Ageing patients with multiple comorbidities (heart disease; diabetic; peripheral arterial obstructive disease) usually have poor and diseased vessels for AVF creation, leading to early failure and/or FTM. At present, there are very few effective therapies for treating AVF nonmaturation.

### Systemic pharmaceutical therapies

Systemic therapies, such as ACE inhibitors, angiotensin-converting enzyme inhibitors, aspirin, prostacyclin and fish oil (FAVOURED study), from small clinical trials and observational studies, have been shown to have the potential to block smooth muscle cell proliferation and migration and to prevent thrombosis in AVFs and AVGs. There has been only one randomised control trial evaluating systemic therapies that target smooth muscle cell proliferation. In that study, clopidogrel (Plavix) reduced the percentage of AVFs with early thrombosis. However, in the more important, clinically relevant endpoint (AVF maturation), clopidogrel did not improve AVF suitability for dialysis, which is defined as cannulation with two needles, minimum dialysis blood flow of 300 ml/min, successful use in eight of 12 dialysis sessions, and use after 120 days from creation. In fact, approximately 60% of AVFs created in both the clopidogrel and placebo group were unsuitable for dialysis use.

### Local pharmaceutical therapies

Local drug delivery therapies have been evaluated as a means of preventing vascular access FTM/dysfunction in AVF and AVG. The clinical and scientific rationale for local perivascular therapies are: 1) perivascular therapies can be easily applied at the time of surgery; 2) perivascular therapies preferentially target the 'active' adventitia, where it is believed that the cells and mediators that play the most important role in neointimal hyperplasia proliferation reside and are initially activated; 3) studies have demonstrated that lipophilic molecules, when perivascularly placed over

the adventitia, rapidly diffuse through all the layers of the vessel wall; and 4) small amounts of potentially toxic drugs can be safely delivered directly at the location of stenosis using the perivascular approach, resulting in high local concentrations with minimal systemic toxicity.

In addition to lining blood vessels, endothelial cells also serve as a 'bioreactor' producing a large number of beneficial mediators that reduce thrombosis, inflammation, stenosis, and increase lumen diameter. Initial experimental studies have documented a beneficial effect of endothelial cell-loaded gel-foam wraps in porcine models of AVF. An early-phase clinical trial using this technology was able to demonstrate technical feasibility and safety in haemodialysis patients who received a "Vascugel®" wrap loaded with treated human aortic endothelial cells at the time of AVF placement.

PRT-201 (Proteon Therapeutics, Waltham, Massachusetts, USA) is a recombinant pancreatic elastase topically applied at the outflow vein at the time of surgery access creation, and which has been shown to result in both arterial and venous dilation and an increase in AVF blood flow in experimental models. Early-phase randomised clinical trials evaluating PRT-201 have demonstrated safety and feasibility, and dose-dependent improved unassisted maturation in radiocephalic AVF. Currently, an ongoing phase-III multicentre, double-blinded, randomised placebo controlled trial is evaluating PRT-201 in radiocephalic AVFs.

A clinical study on the use of liposomal prednisolone was recently started (Lipmat study). Corticosteroids may promote maturation by suppressing inflammation, but have significant systemic side-effects. Liposomal prednisolone has a long circulation time and targets inflamed tissue with low systemic concentrations and limited side effects. In an animal study, it was demonstrated to promote AVF maturation. This study will investigate if liposomal prednisolone is effective in promoting AVF maturation when administered to human subjects after surgical creation of a radiocephalic AVF.

### Endovascular therapies

Balloon-assisted maturation (BAM) usually treats non-dilating veins, while conventional angiography and arterial inflow percutaneous transluminal angioplasty (PTA) treats stenosed forearm arteries. The best results are obtained when the juxta-anastomotic vein and the feeding artery are dilated with 6 and 4 mm dilation balloons, respective-

ly. Rupture of the weak venous or arterial wall is common (15% of cases), the majority of which can be managed with prolonged balloon tamponade. Nonmaturing AVFs are ideally needed only 7 to 14 days after successful dilation to allow haematomas caused by cannulation and local anaesthesia to resorb. Including initial failures, 1-year primary and secondary patency rates reported by interventional radiologists range from 34% to 39% and 68% to 79%, respectively. Results after dilation of diseased radial arteries feeding normal veins are even better, with primary patency rates ranging from 65% to 83%, and secondary patency rates to over 90%. BAM can be performed with conventional angiographic techniques or under ultrasound guidance.

### Surgical therapies

Suboptimal haemodynamics, variable surgical skills, and technique dependency are widely believed to contribute to AVF nonmaturation. The Optiflow (Bioconnect Systems, Ambler, Pa) is a novel anastomotic device placed in situ that has potential for improving haemodynamics and standardizing AVF creation. A prospective nonrandomised controlled pilot study designed to investigate the safety and performance of the Optiflow in 41 patients and 39 matched control participants underwent AVF formation using the standard technique at two sites. The primary endpoint was unassisted maturation, which was defined as an outflow vein with a diameter 5 mm and blood flow 500 ml/min measured by Doppler ultrasound. The secondary endpoint was unassisted patency, and the primary safety endpoint was freedom from device-related serious adverse events. Unassisted maturation rates at 14, 42, and 90 days were 76%, 72%, and 68%, respectively, for the Optiflow group and 67%, 68%, and 76%, respectively, in the control group (P .38, .69, and .47 at 14, 42, and 90 days). There was a trend to earlier maturation (assessed at 14 days) in the Optiflow group compared with the control group (P 0.059). ■

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