An interview with Professor Bo Feldt-Rasmussen, congress president

Nephrology faces many challenges. We adhered to the motto of the 2018 ERA-EDTA Congress – Kidney disease – new paradigms, new challenges. New challenges, new opportunities. The scientific program will make the underlying many of them: Once you have kidney disease which is life-threatening in the long run, even in transplanted patients. Additionally, we have to widen our focus, forming multidisciplinary teams and holding case conferences, thus bringing our expertise into neighboring disciplines as well – this is the way to strengthen internal medicine and lead it to the highest standards of excellence.

To what extent does your choice of plenary speakers mirror the overarching theme of the Congress?

The four plenary lectures are all very different, yet they all relate to the Congress theme. The first is on gene editing, which is a powerful new tool for nephrology research and therapy. It will be delivered by Toni Cathomen, from Freiburg in Germany, as part of the Welcome Ceremony. The second one looks into the very close link between kidney disease and cardiovascular disease, which is extremely important for our patients. I also know...
Kidney disease — new paradigms, new challenges. New challenges, new opportunities

An interview with Professor Bo Feldt-Rasmussen, congress president of the 2018 ERA-EDTA Congress

Professor Bo Feldt-Rasmussen, can you explain the overarching theme or "motto" of the 2018 ERA-EDTA Congress?

Nephrology faces many challenges. We address these in the theme of this year’s Congress "Kidney disease – new paradigms, new challenges. New challenges, new opportunities". The scientific program will make the basic ideas behind the theme come to live. We present new paradigms/new ways of thinking and arguing disease mechanisms. New techniques including molecular biology and genomic medicine – which both investigate the smallest details of the physiology and function of the human body will be discussed. Using “big data” and “genome-based medicine”, bring new insights and opportunities towards a more “personalized” treatment in nephrology. These new paradigms and opportunities are crucial in our ongoing search for better treatment for our patients.

Why are new forms of treatment necessary? Well, we do not have a cure for many renal diseases and a cure is something we should be striving for! Then perhaps one day we will need renal replacement therapies in only few patients. Of course, this sounds very ambitious, especially because patients lose kidney function due to many different diseases. But there seems to be one pathomechanism underlying many of them: Once you have kidney damage of a certain severity, the kidney continues to lose function, regardless of which disease made the initial attack. The progress cannot be stopped – and we need to target this problem. If we could find a cure to stop progression, we would be able to prevent end stage renal disease and the need for renal replacement therapy in many patients.

What are the general challenges you referred to and that nephrology faces? One of the major challenges in nephrology is that our patients suffer from a very severe disease which is life-threatening in the early stages, chronic kidney disease is in its more advanced stages relatively rare. Therefore, one major challenge facing nephrology is to acquire the necessary funding and support from the pharmaceuticals industry for the clinical trials that are needed to test new treatments. Even when there is a treatment principle that we believe works, it really costs a lot of money to test it properly – and the industry is often unwilling to fund these studies, because they are worried about not getting a proper return on their investment. There is also the question of statistical power. In randomized trials on hypertension or diabetes, there are often 10,000 patients and numbers we cannot compete with.

Another challenge is multidisciplinarity. I genuinely believe that we have to collaborate closely with cardiologists, endocrinologists, rheumatologists, and so on, if we are to get the best results for our patients. We are the experts for kidney disease, of course, but we have to widen our focus, form multidisciplinary teams and hold case conferences, thus bringing our expertise into neighboring disciplines as well – this is the way to strengthen internal medicine and lead it to the highest standards of excellence.

To what extent does your choice of plenary speakers mirror the overarching theme of the Congress? The four plenary lectures are all very different, yet they all relate to the Congress theme. The first is on gene editing, which is a powerful new tool for nephrology research and therapy. It will be delivered by Toni Cathomen, from Freiburg in Germany, as part of the Welcome Ceremony. The second one looks into the very close link between kidney disease and cardiovascular disease, which is extremely important for our patients. I also know...
that the speaker, my Danish colleague, Klaus Olsen, will be taking a slightly different angle and will approach the topic in an innovative, if not surprising way, from which I am sure the audience will benefit greatly. The title of the third plenary lecture is “From the RNA world to the clinic: RNAs as drugs and drug targets” and will be delivered by Bruce Suel- lenger, from Durham, U.S.A. Expectations regarding RNA sequencing are high, and there is hope of finding relevant biomarkers that provide insight into the nature of kidney diseases. The fourth plenary lecture will be delivered by Marcello Tonelli, from Calgary in Canada, and deals with the epidemiology of kidney disease, which in a way, is one of the challenges nephrology faces.

Apart from the plenary lectures, what are the main highlights of the scientific program, in your personal opinion? The program is structured into nine tracks. In each track, there will be symposia, mini-lectures, free communications and posters. This means a wealth of topics and sessions, but due to the structure it should be easy for everyone to find the topics they are interested in and which cover their particular areas of expertise. Personally, I am very interested in the topics of diabetes, especially its metabolic aspects, and cardiovascular disease.

But apart from that there are other sessions for which I am of general interest, I think. For the first time we have a symposium with the catchy title “Nephrology Pearls”, in which the state of the art in five areas will be presented: 1) Basic Science and Translational Nephrology; 2) Epidemiology and Clinical Nephrology; 3) ESKD and Dialysis; 4) Kidney Transplantation, and 5) Hypertension and Diabetes. You definitely should not miss this one! And then we have the “late breaking clinical trials”, the best abstracts and posters – and the many joint sessions with other associations, such as the Hypertension Society, the Japanese Nephropathy Society, the Chinese Nephrology Society – not forgetting the special sessions of the ERA-EDTA Registry and the one on ASN Highlights.

What do you think makes this Congress especially attractive for young nephrologists? First of all, the program, and I really think that structuring it into thematic tracks makes it easy to find one’s bearings. The Young Nephrology Platform will also be offering special educational activities which will be of particular interest to the younger audience. But I think the most important thing the Congress offers is the opportunity to network. Young doctors can meet whomsoever they would like to meet to discuss their own research projects and career perspectives. This personal contact is invaluable, and I believe it cannot be compensated for with any modern media tools.

To what extent does the scientific program reflect Danish topics and speakers? The Danish Society of Nephrology is the co-partner of this ERA-EDTA Congress. In that capacity, it has planned and organized nine symposia, which is a lot. Many Danish nephrologists have been involved – and this might be the reason why Danish nephrologists are among the top ten abstract submitters, which is a great success, considering the size of our country! I am very proud and excited that Danish nephrology will gain so much visibility during this Congress.

Speaking of Denmark – what should participants from abroad who are in Copenhagen for the first time make sure they see or do (apart from attending the Congress)? First of all, everyone should take part in the “Renal Run”. It starts just outside the Bella Center, our congress center, and is organized in such a way that taking part is very comfy (with facilities to freshen up and change after the run). The proceeds will be given to “Medicines sans frontières”, so this should really be an incentive for many Congress delegates to take part!

Then of course, it is very easy to take the metro into the city center, which is only a couple of stops away. We have the “Old Copenhagen” quarter with all its buildings and castles, and I am sure that people will enjoy it, as well as the harbor and the seaside. There are many art galleries and museums, nice shops and good restaurants from cheap to expensive. In culinary terms, Denmark has much more to offer than “Røde Pølser” (“red sausages”), the “Nordic Cuisine” has become quite renowned these days. Biking around in Copenhagen is very popular, too, and easy to do. You can grab a rental bike at nearly any corner and explore the city. Besides, Copenhagen has the reputation of being a cool city with a special atmosphere: relaxed and cozy, or “hyggelig” as we say in Denmark.

It is my great pleasure and honor to welcome all of you to Copenhagen and to the Congress. I am sure its scientific sessions and symposia are as attractive as our charming city. I wish all those taking part a wealth of interesting contributions and discussions!
Inflammation in crystal nephropathies

Understanding the injury is the first step towards cure

The entity of crystal nephropathies encompasses a spectrum of different kidney injuries induced by crystals formed from intrinsic minerals, metabolites and proteins, or extrinsic dietary components and drug metabolites. Depending on the localization and dynamics of crystal deposition, the clinical presentation that suggest that there is also a role for mitochondrial permeability transition-related regulated necrosis. Type 3 is represented by crystal and stone formation in the draining urinary tract (i.e. urolithiasis), causing renal colic and chronic obstruction.

Dissecting the types of injury is the first step towards a better understanding of the pathophysiology of crystal nephropathies. Crystal-induced activation of the inflammasome and necroptosis, crystal adhesion, crystallization inhibitors, extratubulation and granuloma formation are only a few of certainly many involved pathomechanisms that deserve further study to eventually form the basis for innovative cures for these diseases.

Balancing remission against side effects

Cyclophosphamide in minimal change disease and focal segmental glomerulosclerosis

Minimal change disease (MCD) is a typical disorder of children that responds very well to corticosteroids. However, 50–60% of responders may have frequent relapses or may become steroid-dependent. Repeat or continuous administration of corticosteroids causes severe toxicity in these patients. Cyclophosphamide (CYC) has been the first steroid-sparring drug used in MCD. CYC may maintain remission at two years in about 70% of frequent relapers (2 mg/kg/d for 8 weeks) and 65% of steroid-dependent children (2 mg/kg/d for 12 weeks). However, it may be unsafe to repeat CYC in the case of further relapses, because of the risk of severe side effects. A number of alternative steroid-sparring treatments are available, including calcineurin-inhibitors, mycophenolate, and/or rituximab.

Table 1

<table>
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<tr>
<th>Measures to prevent cyclophosphamide (CYC) toxicity</th>
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<tr>
<td><strong>Bladder</strong></td>
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<tr>
<td>・ Forced hydration (diuretics if oliguria)</td>
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<tr>
<td>・ Frequent voiding</td>
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<tr>
<td>・ Do not exceed 25 g (risk of bladder fibrosis)</td>
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<tr>
<td><strong>Bone marrow</strong></td>
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<tr>
<td>・ Halve the dose if WBC &lt; 3,000/cmm</td>
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<tr>
<td>・ Transiently stop CYC if WBC &lt; 3,000/cmm</td>
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<tr>
<td><strong>Gonadal toxicity</strong></td>
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<tr>
<td>・ The gonads are more resistant in young patients</td>
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<tr>
<td>・ In males do not exceed a cumulative dose of 250–300 mg/kg in children or 168 mg/kg in adults</td>
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<tr>
<td>・ In females do not exceed dose of 20 g (if the patient 20 years old), 5 g (if 30 years old), 9 g (if 40 years old). Gonadotropin-releasing hormone agonist if prolonged used of CYC</td>
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Idiopathic focal segmental glomerulosclerosis (FSGS) may respond to a prolonged use of corticosteroids in 55–60% of cases. CYC may obtain remission in a consistent number of patients when given as a first treatment (usually associated or alternated with corticosteroids) and may maintain remission for about 70% of frequent relapers or 65% of steroid-dependent children (2 mg/kg/d for 12 weeks). However, it may be unsafe to repeat CYC in the case of further relapses, because of the risk of severe side effects. A number of alternative steroid-sparring treatments are available, including calcineurin-inhibitors, mycophenolate, and/or rituximab.

In summary, CYC may maintain prolonged remission in many patients with frequent relapses or steroid-dependency, but it is of little efficacy in steroid-resistant patients. A main issue with CYC is represented by its toxicity. CYC is a prodrug that is metabolized by cytochrome P450 to hydroxy-CYC. This is interconverted to aldophosphamide, which is catalobolized to inactive carboxy-CYC by an aldohexide dehydrogenase. A certain amount of aldophosphamide that escapes the effects of dehydrogenase is converted to acrolein and phosphoramide mustard, an agent that adds alkyl groups to oxygen and nitrogen atoms of guanine, one of the four nitrogen bases that form the DNA nucleotides. As a result, guanine loses its affinity for cytosine and binds to thymine, causing DNA cross-links and introducing DNA breaks. These cytotoxic and mutagenic effects mainly occur in proliferating cells, while repair mechanisms may prevent DNA damage in quiescent cells. However, the repair mechanisms may be insufficient to counter the side effects of CYC if a high dose of the drug is used.

The toxicity of CYC is mainly exerted on certain tissues. The acrolein can produce hemorrhagic cystitis and even bladder fibrosis when given for prolonged periods. Other adverse events are related to phosphoramide mustard and are dose- and age-dependent. Blood cells that have an active metabolism are particularly vulnerable to the adverse events of CYC. Gonadal toxicity may result in oligospermia or azoospermia in males (not always reversibel) and ovarian failure in females. Leukemia, bladder cancer and other types of malignancy may occur. A number of precautionary measures should be taken to prevent these untoward events (Table). In conclusion, CYC is a cheap drug that may maintain a stable remission in steroid-sensitive patients with MCD/FSGS but it may lead to severe side effects. A dose monitoring of blood count and clinical conditions, as well as low cumulative doses of CYC, are strongly recommended when using it in patients with MCD or FSGS.
Although there is no question that cerebral stroke and systemic embolization (SSE) in patients with atrial fibrillation (AF) via oral anticoagulant therapy (OAT) follows stringent guideline-based recommendations. Large-scale randomized clinical trials (RCT) found that patients with at least a moderate risk of SSE (defined as a CHA2DS2-VASc score of ≥2 in men and ≥2 in women) should receive OAT, as the benefit of SSE prevention outweighs the bleeding risk in these patients. In contrast, SSE prevention is less evidence-based in advanced chronic kidney disease (CKD) patients, even though AF is more prevalent. As AF patients with advanced CKD are at higher SSE risk than AF patients with intact renal function, they should particularly benefit from OAT. Unfortunately, however, bleeding risk on anticoagulation therapy also increases substantially in advanced CKD.

Unlike in the general population, no RCT has analyzed the efficacy (i.e., prevention of thromboembolic events) and safety (i.e., no major bleeding events) of vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs) in advanced CKD (e.g., in patients with a glomerular filtration rate [GFR] < 30 ml/min/1.73 m² or on dialysis). For patients with less advanced CKD, subgroup analyses are available from a single RCT, which found much fewer strokes in CKD stage G3a/G3b patients on adjusted-dose warfarin than in those patients on low-dose warfarin plus aspirin. In the absence of RCTs, several groups have conducted retrospective cohort analyses with administrative registry data in order to analyze the benefit of OAT in advanced CKD. In non-diagnosis CKD patients with AF, an evident benefit of OAT has been found. For dialysis patients, however, these analyses yielded conflicting findings: some early analyses suggested no benefits of OAT because the stroke risk was not reduced in the total cohort, and in elderly patients, the stroke incidence even increased with OAT. In contrast, others found a benefit of anticoagulation in terms of effective risk reduction for strokes. As a limitation, most published registry analyses of OAT among CKD patients with AF collected data in an era when few patients received NOACs. These surprising results might be explained by experimental data that imply that traditional OAT with VKA may propagate vascular calcification. Additionally, epidemiologic data suggest that patients on VKAs with poor INR control suffer accelerated CKD progression (and subsequently higher cardiovascular event rates), as overdosing may result in nephron loss because of repetitive subclinical bleeding episodes. Meanwhile, large-scale clinical trials found NOACs in the general population to be at least as efficient as VKA for the SSE prevention and at least as safe—particularly with regard to intracranial bleeding. Notably, subgroup analyses from these large NOAC trials prove noninferiority (partly even superiority) of all approved NOACs compared with warfarin in patients with mild to moderate CKD (down to patients with a creatinine clearance of ≥25 to 30 ml/min).

Two ongoing studies aim to compare NOACs and VKAs in patients with CKD stage G5, and we encourage all our German colleagues to participate in the German XAVIA study (contact E-Mail: juergensmeyer@af-net.eu). Until these data are available, the lack of evidence precludes strong recommendations in favor of or against NOACs in CKD stage G4 and in dialysis patients, which is reflected in slightly different recommendations regarding NOAC use by European and US authorities. In particular, one NOAC (apixaban) has been licensed for use among dialysis patients by the US Food and Drug Administration but not (yet) in Europe. Compared with other licensed NOACs, apixaban depends less on renal excretion for its elimination. Therefore, apixaban has a lower risk of accumulation in advanced CKD, but still requires adjustment for renal function. Of note, pharmacokinetic studies (and subsequent recommendations of NOAC doses) still focus on creatinine clearance (estimated with the Cockcroft-Gault equation), whereas nephrologists are today accustomed to estimate the GFR with the CKD-EPIcrea equation. Substituting the latter for the former may cause large dose errors. For the time being, we suggest as a potential consensus for CKD patients with AF and at least a moderate risk of thromboembolism (defined by a CHA2DS2-VASc score ≥2 for women and ≥1 for men), to preferably offer NOACs in CKD stage G3a/3b, to offer either NOACs or VKAs in CKD stage G4, and to choose on an individual basis between VKAs, NOACs, heparinization (with subcutaneous injection of low-molecular weight heparins on non-dialysis days) and no anticoagulation in CKD stage G5 patients.

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The scientific community is called to action and date
A plea for more prevention
The health economics of chronic kidney disease

In addition, costs for CKD are not limited to RRT, but also include non-renal health-care costs, costs unrelated to health care, and costs for patients with CKD who are not yet receiving RRT. Even if patients with CKD or ESRD could be given the least expensive therapies, costs would decrease only marginally. We therefore propose a consistent and sustainable approach focusing on prevention. Before a preventive strategy is favored, however, authorities should carefully analyze the cost-to-benefit ratio of each strategy. Primary prevention of CKD is more important than secondary prevention, as many other chronic diseases, such as diabetes mellitus, hypertension, cardiovascular disease, liver disease, cancer, and pulmonary disorders, could also be prevented in the same effort. Reversible conditions leading to these chronic diseases are often common to many disorders, with CKD at the final stage.

Primary prevention largely consists of lifestyle changes that will reduce global societal costs and, more importantly, result in a healthy, active and long-lived population. Those measures include the promotion of exercise, the reduction of obesity, smoking and environmental pollution, and a host of dietary measures. Although for each of these options exemplary approaches could be shown, I will restrict my presentation to dietary measures.

Most processed foods available in the retail sector are supplemented with unnecessary quantities of salt and glucose. It was calculated that if all Germans were to ingest the recommended quantities of salt and sugar, health care costs would decrease by €16.8 billion per year, i.e. 2.1 billion per 10 million people. It is difficult to check food contents from food labels, if the latter are available at all. In addition, the majority of people do not use them, even if they suffer from a risk factor like hypertension. Simplified food labels are not harmonized throughout Europe and not available in several countries. Another often-neglected aspect is education, which should focus on children and on people with limited financial resources or education, who are more vulnerable to chronic disorders. Authorities should also focus on food regulation, rather than leaving the initiative to self-regulation by providers.

In conclusion, combating chronic diseases by primary prevention to improve lifestyle should result in socio-economic benefits for societies, including reduction of CKD and ESRD. Ne-phrologists need to collaborate closely with other sectors and governments, to reach these aims.

Figure 1: Collaborative Effort © Vanholder
Don’t forget to vote!
for the new ERA-EDTA Council members

The voting station, located in the Registration area of the Bella Center, will be open only on 25 May 2018 and will follow this schedule: 9.30–10.45 and 16.30–17.00. Voting will also be possible immediately before the start of the General Assembly, which will take place from 09.30–10.45, 26 May 2018, in room C1-M5 of the Bella Center.

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.
Insulin resistance is typically defined as decreased biological action of insulin at its target organs (e.g., skeletal muscles) for any given blood concentration of insulin. Clinically insulin resistance usually presents with hyperinsulinemia, glucose intolerance and hyperglycemia.

There are a number of well-established direct and indirect methods for the quantification of insulin resistance that vary in complexity. By using the ‘gold standard’ euglycemic clamp technique, an inadequate target cell-response to the actions of insulin in patients with CKD was recognized decades ago [1]. Since then, many studies have revealed that insulin resistance is already present in non-diabetic CKD patients at the earliest stage of kidney impairment, i.e. even before GFR is significantly decreased [2]. The causal nature of insulin resistance in CKD is still poorly defined, however.

Abnormal peripheral insulin sensitivity may at least partly explain the conflicting results. Nevertheless, addressing this issue is of major interest because cardiovascular complications are a significant cause of mortality in CKD patients.

References
03. Am J Physiol 1999;276:E78 – 84
The objective of all diagnostic and therapeu- tic decisions taken by clinicians in the care of patients is to improve prognosis by preventing or modifying the natural evolution of the disease. Therefore, prognostic research is an important area of investigation in clinical epidemiology. Prognostic research focuses on the prediction of the future course of a given disease in probability terms. Prognostication is performed by clinicians using risk prediction rules that allow us to estimate the probability that a specific event occurs in a given patient over a predefined time period conditional on prognostic factors.

Before being applied in clinical practice, risk prediction rules should be validated by assessing their discrimination, calibration, explained variation and risk reclassification. Discrimination measures how well a prognostic model distinguishes (discriminates) patients with and without the outcome of interest (for example, patients who died versus those who survived).

Discrimination, as measured by the Harrell’s C-index, may take values ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination). The higher the Harrell’s C-index, the greater the accuracy of the model in predicting the event of interest. Calibration measures how far the prognostic estimate of a predictive model including one or more biomarkers matches the ‘real’ probability of the outcome (i.e., the observed proportion of an event in a given time period). In calibration analysis, predicted and observed probabilities of a certain event are compared by the Mayo-Hosmer Test. A non-significant Mayo-Hosmer Test indicates that predicted and observed probabilities of the event do not differ and that the calibration of the model is satisfactory.

Another statistical technique for assessing the validity of a risk prediction model is assessing the explained variation in a given outcome, a method which combines calibration and discrimination. Explained variation compares predictive inaccuracy between models with and without predictors. A value of 100% would indicate that the outcome status can be predicted perfectly, while a value of 0% means that the predictions are meaningless. Reclassification analyses allow us to evaluate the gain in risk prediction accuracy by using a new model compared with an established one. The analysis of risk reclassification can be performed by net reclassification index (NRI) or integrated discrimination improvement (IDI), and quantifies whether a new biomarker provides a clinically relevant improvement in the accuracy of prediction above and beyond that provided by a model not including the new candidate prognostic biomarker. The basic idea behind the risk reclassification is that a valuable new biomarker will increase the predicted risk for patients with the event of interest and will decrease predicted risk for patients without such event.

During my lecture I will discuss the concepts of developing and validating risk prediction models by means of several examples extracted from the literature. The concept of internal, external and temporal validation will be also discussed.

Deceased-donor kidneys: quality is worsening

In order to meet the demand for transplantable kidneys, an increasing number of marginal donors are being utilized. We were curious to see over a 10-year period, the degree to which the quality of deceased-donor kidneys had worsened, and if this had affected kidney transplant survival outcomes. But how does one determine the quality of a deceased-donor kidney?

The kidney donor risk index (KDRI), calculated from 10 deceased donor factors, estimates how long a deceased-donor kidney allograft can be expected to function, relative to the median deceased-donor kidney retrieved in the United States in the previous calendar year. Therefore, we used the KDRI as a marker of kidney quality.

We calculated the KDRI scores of all deceased-donor kidney transplants – approximately 24,000 – between 2005 and 2015 in seven European countries reporting data to the ERA-EDTA Registry. We then standardized all these KDRI scores to the median deceased-donor KDRI score in 2005. By doing so, we created a baseline from which we could compare the other KDRI scores. We then investigated trends in the KDRI over the 10-year period, especially in specific subgroups such as young or old transplant recipients, men versus women, and across countries.

During this time period, the overall quality of deceased-donor kidneys decreased for every recipient group with the exception of the younger transplant recipients aged 18–44 years. We found that these changes in the KDRI score (and by proxy kidney quality) were predominantly driven by an increased use of older deceased donors, donors with a prior diagnosis of hypertension or diabetes mellitus, and for the some countries the use of circulatory-death donors. We also saw differences in the median KDRI across the seven European countries, with some having consistently lower KDRI’s (by proxy better-quality deceased-donor kidneys) and some countries consistently higher KDRI’s.

One would expect to see that, as a result of worsening deceased-donor kidney quality, kidney graft survival would also worsen. However, interestingly, despite the deterioration in the overall quality of deceased-donor kidneys over time, there was no change in the five-year patient and graft survival outcomes.

Given the long-standing shortage of deceased-donor kidneys it is likely that the trend of worsening deceased-donor kidney quality will continue. Luckily, at this point it has not affected medium-term (five-year) survival. However, to avoid this deterioration in quality translating at some point into worsening survival outcomes, the transplant community should focus on other methods of preserving kidney allograft quality, including preservation techniques, reducing cold ischemia time and improvements to immunosuppression regimens.

We would like to thank the patients and the staff of the dialysis and transplant units for contributing the data via their national and regional renal registries to the ERA-EDTA Registry.

References
Professor Jürgen Floege is the recipient of the 2018 ERA-EDTA Award for Outstanding Clinical Contributions to Nephrology.

Professor Jürgen Floege received his clinical training at the Hannover Medical School, Germany. His particular interest in renal diseases developed during various research periods in physiology, pharmacology, nephrology and pathology at the Hannover Medical School, Germany, the Albert Einstein College of Medicine, New York and the University of Washington, Seattle, USA. He was appointed as head of the Division of Nephrology and Immunology at the University of Aachen, Germany in 1999. Professor Floege is a former vice dean in Aachen, executive council member of the ERA-EDTA and International Society of Nephrology (ISN) and current member of the executive board of KDIGO, a society developing world-wide nephrology guidelines.

He is immediate past-president of the German Society of Nephrology as well as honorary member of the Japanese, Polish, Portuguese, Serbian, and Slovakian Societies of Nephrology. In 2017 he was elected into the council of the German Society of Internal Medicine, Europe’s largest professional medical society, and is President-elect of that society for 2019.

Prof. Floege’s major scientific accomplishments are the development of a novel scintigraphic method to diagnose dialysis amyloidosis, clarification of the role of various growth factors and cytokines in renal disease and identification of novel mechanisms of vascular and soft tissue calcification – in particular the roles of fetuin-A and vitamin K in CKD. He has also been the creator and leader of the investigator-initiated STOP-IgAN trial and has contributed to numerous other major trials in glomerular disease and CKD-MBD.

Prof. Floege has authored and co-authored more than 500 scientific articles, reviews and monographs. He has patented methods to diagnostically treat amyloidosis specifically and a method for the treatment of nephritis using anti-PDGF-D antibodies. Together with Professors Richard Johnson, Marcello Tonelli and John Feehally he edited the best-selling textbook “Comprehensive Clinical Nephrology”, now in its 6th edition. Finally, Professor Floege is associate editor of Kidney International since Jan 2018 and currently a senior editor of the World Journal of the American Society of Nephrology, Nature Reviews Nephrology, Journal of Nephrology and others.

Prof. Floege has chaired, co-chaired and organised several congresses of ERA-EDTA, the American Society of Nephrology and World Congresses of Nephrology. He is an honorary member of the Japanese, Polish, Portuguese, Serbian, and Slovakian Societies and a Fellow of the American National Kidney Foundation.

In 2011 Prof. Floege was recognised as a Distinguished Fellow of ERA-EDTA (FEFA).

Professor Hans-Joachim Anders is the recipient of the 2018 ERA-EDTA Award for Outstanding Basic Science Contributions to Nephrology.

Professor Hans-Joachim Anders currently heads his own laboratory at the University of Munich. His qualifications are in the field of internal medicine, nephrology and rheumatology.

Prof. Anders is a physician scientist whose research focuses on translational aspects of kidney disease. His major scientific achievements include innovative pathophysiological concepts related to innate immunity in kidney diseases – such as “necroinflammation” in AKI or the pathophysiology of lupus nephritis. Recently, he started to explore the molecular pathophysiology of crystal-related kidney diseases. Prior to this, he had conducted essential preclinical studies on the role of chemokine receptors, Toll-like receptors, and inflammasomes in AKI and CKD as well as successful preclinical validation of compounds later confirmed by clinical trials of lupus nephritis and diabetic kidney disease.

Prof. Anders has authored more than 290 publications. He is currently associate editor of the Journal of the American Society of Nephrology and Nephrology Dialysis Transplantation and has served or serves as a member of the editorial boards of the Clinical Journal of the American Society of Nephrology, Kidney International, BMC Nephrology and Nature Reviews Nephrology.

Prof. Anders has been very active in ERA-EDTA. He served as a congress secretary in the annual meeting in 2010 and in various boards. He is a current board member of the Immunonephrology Working Group and he has been a long-term member of the Scientific Advisory Board (SAB) before he became its Secretary Coordinator in 2015.

Prof. Anders was recognised as a Distinguished Fellow of ERA-EDTA (FEFA) in 2014.

Professor Andrzej Więcek is the recipient of the 2018 ERA-EDTA Award for Outstanding Contributions to ERA-EDTA.

Prof. Andrzej Więcek has been an ERA-EDTA member for 30 years. In 1999, he was elected to the ERA-EDTA Council and he was re-elected for the second term in 2006. In 2011, he became Secretary-Treasurer of our Society. In 2014, he was elected the ERA-EDTA President. He was instrumental in promoting the very successful ongoing collaboration with ASN and ISN. He also strongly supported ERA-EDTA; collaboration with the National Societies as well as other societies (JSN, CSN, ESC, ESH, IAHN, etc.). He has been an active member of many ERA-EDTA bodies including ERA-EDTA Scientific Advisory Board (Chair 2014–2017), the European Renal Best Practice Board, EURECAM Board, Eutox Board and ERA-EDTA Registry Committee.

He has been a member of the Editorial Board of Nephrology, Dialysis, Transplantation since 1999 and its Theme Editor since 2001. Prof. Wieczek has been very influential in the Society and he presented many innovative activities. During his presidency, he stabilised the Society’s financial situation, led the reorganisation of the office in Parma and increased the number of ERA-EDTA members. During the period between 2000–2002, he was responsible for CME courses as the new ERA-EDTA initiative. In 2011, he initiated the Young Nephrologist Platform. He helped to launch the ERA-EDTA Activation Committee. He came up with the idea of the ERA-EDTA Virtual Museum and he is its first Curator. Prof. Wieczek represented ERA-EDTA as the speaker during the ERA-EDTA Highlight sessions of the ASN Kidney Weeks in 2014 and 2017. He was ERA-EDTA Congress Co-President in London (2015), Vienna (2016) and Madrid (2017).

Prof. Wieczek came up with the idea of ERA-EDTA logo’s new strapline “Leading European Nephrology”. In 2011, Prof. Wieczek was recognised as a Distinguished Fellow of ERA-EDTA (FEFA).

Doctor Shrikant Ramesh Mulay is the recipient of the 2018 ERA-EDTA Stanley Shaldon Award for Young Investigators.

Dr Mulay finished his education in Pharmacology & Toxicology at the National Institute of Pharmaceutical Education and Research (NIPER) Mohali in India in 2009. He conducted his doctoral research on the role of murine double minute (MDM)-2 in kidney injury and repair at Ludwig Maximilians University of Munich (LMU) in 2013. He became post-doctoral research fellow and principal investigator at the local Division of Nephrology. Since 2017, he has been Priv. Doz. (Assistant Professor) at LMU Faculty of Medicine, Medical Clinic and Polyclinic IV.

He leads the research group aiming to understand complex renal pathologies. He is focused on exploring the role of innate immunity and inflammation in acute and chronic kidney diseases in order to find novel therapeutic strategies. He has presented his findings during ERA-EDTA and ASN Congresses several times.

He has published 45 research articles, of which 23 are as the first or last author. His articles have been published in prestigious journals such as The New England Journal of Medicine, Nature Communications, Nature Reviews Nephrology, Journal of Clinical Investigation, Kidney International, Journal of the American Society of Nephrology and Nephrology, Dialysis, Transplantation. He raised research funds of around € 0.55 Million from the German Research Council (DFG) and industry collaborations.

As the winner of the Stanley Shaldon Award, Dr Shrikant Ramesh Mulay will also become an ex-officio member of the Young Nephrologists’ Platform Board.
The prevalence of obesity among end-stage kidney disease (ESKD) patients is on the rise. Despite a wealth of evidence suggesting that obesity portends better outcomes among patients on dialysis, many centers place restrictions on selecting obese patients for kidney transplantation because of concerns over immediate complications or worse long-term outcomes. Indeed, obesity may increase the risk of delayed graft function or wound infections; on the other hand, however, selected obese patients can achieve good outcomes and may experience a survival benefit with transplantation compared with dialysis. To overcome the contradictions of the impact of obesity on individual outcomes in kidney transplant candidates, the DESCARTES ERA-EDTA working group has embarked on the initiative of producing a comprehensive guidance document with the methodological support of the ERBP (European Renal Best Practice) group, the leading ERA-EDTA body in renal recommendations.

There are indeed some ‘hot’ questions in this topic that deserve to be addressed by a rigorous evidence-based approach. For instance, it is still unclear whether body mass index (BMI) remains the best method to evaluate obesity as a risk factor before transplantation, particularly when compared to other ‘alternative’ indexes such as waist circumference, waist-hip ratio, conicity index or total body fat measurement. No less important, it should also be clarified the degree to which obesity has a true influence on mortality, peri-/post-operative complications and other ‘key’ outcomes, including cardiovascular morbidity and quality of life.

The optimal management of obese transplant candidates is also a source of debate. In the general population, different strategies exist to achieve weight loss; these include dietary, behavioral, exercise, as well as drug and surgical approaches, alone or in combination. In this particular population, it becomes of foremost importance to ascertain whether one approach should be recommended over another, particularly taking into account possible harms and sequelae of pharmacologic therapies or bariatric surgery.

Findings from this ambitious initiative are expected to be soon made available to the European nephrology audience (and, hopefully, beyond). They will certainly be helpful in im-
proving the clinical management of ESKD patients, as well as in creating standardized approaches and clinical decisions in obese/overweight individuals who are potential candidates for kidney transplantation.

◘ Magnesium is most important in the process of release of chemical energy. Although most magnesium is stored out of the extracellular fluid compartment, the regulated value is blood magnesium concentration. Cell and bone magnesium do not play a major role in the defense of blood magnesium content and concentration; the major role is played by the kidney, where the renal tubule matches the urinary magnesium excretion and the net entry of magnesium in the extracellular fluid. In the kidney, magnesium is reabsorbed in the proximal tubule, the thick ascending limb of the loop of Henle and the distal convoluted tubule. Magnesium absorption is mainly paracellular in the proximal tubule and in the thick ascending limb of the loop of Henle, whereas it is transcellular in the distal tubule.

The molecular mechanisms responsible for normal renal magnesium handling, as well as the many factors able to affect renal magnesium handling, will be described. The emphasis will be put on the role of claudin proteins expressed at the tight junction of the thick ascending limb of the loop of Henle, as well as on membrane proteins relevant to transcellular magnesium transport in the distal convoluted tubule. The roles of parathyroid hormone, epidermal growth factor and the calcium/magnesium-sensing receptor will be detailed.

Finally, the main mechanisms of abnormal renal tubular transport of magnesium that affect overall magnesium homeostasis in humans will be described. Abnormal magnesium transport can result from a disorder of paracellular transport in the thick ascending limb of the loop of Henle or of transcellular magnesium transport in the distal convoluted tubule. Depending on the specific molecular mechanism, the renal handling of other electrolytes (e.g., Na, K, Ca) can also be altered, resulting in distinctive biological syndromes.

◘ EDUCATION
Magnesium and the kidney
Mechanism and regulation of renal magnesium transport: clinical implications

PASCAL HOUILLIER
Paris, France

Magnesium is most important in the process of release of chemical energy. Although most magnesium is stored out of the extracellular fluid compartment, the regulated value is blood magnesium concentration. Cell and bone magnesium do not play a major role in the defense of blood magnesium content and concentration; the major role is played by the kidney, where the renal tubule matches the urinary magnesium excretion and the net entry of magnesium in the extracellular fluid. In the kidney, magnesium is reabsorbed in the proximal tubule, the thick ascending limb of the loop of Henle and the distal convoluted tubule. Magnesium absorption is mainly paracellular in the proximal tubule and in the thick ascending limb of the loop of Henle, whereas it is transcellular in the distal tubule.

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Figure 1: Schematic chart diagram for the diagnosis of hypomagnesemia
UMgV: urinary magnesium excretion; UCaV: urinary calcium excretion; TAL: thick ascending limb of the loop of Henle; DCT: distal convoluted tubule © Houillier

CME 8
Electrolytes and acid-base balance: from physiology to clinic
Thursday, 08.45 – 12.00, C1-M5
Hypokalemia: a clinical perspective
Considering normal and abnormal potassium homeostasis

The distribution of body potassium (K+) contrasts strikingly with that of sodium (Na+); whereas Na+ is predominantly extracellular, K+ is intracellular (~98%; ~3,500 mmol) and is the most abundant intracellular cation (HPO4 being the most abundant anion). A high intracellular K+ is necessary for regulation of cell volume, pH, enzyme function, DNA and protein synthesis, and cell growth. A low extracellular K+ (plasma or serum K+; SK) and the associated steep K+ gradient across the cell membrane are largely responsible for the membrane potential of excitable and non-excitable cells; any change in this gradient can disturb cell excitation and contraction: a doubling or halving of SK will have this effect.

Chronic K+ depletion causes an impaired concentrating ability, a tendency to metabolic alkalosis, increased ammonium (NH4+) excretion and magnesium (Mg2+) loss. More recently, interest has focused on the importance of and ways in which SK levels can influence distal nephron function. I will try to illustrate how to apply some of these physiological principles in presenting and discussing some relevant clinical examples.

Normal K+ homeostasis depends on extrarenal balance – intake (80–120 mmol/day) versus excretion (urine + breath); and intrarenal balance – distribution of K+ between intracellular (IC; mostly in skeletal muscle cells) and extracellular compartments (EC). Note that as low a shift of 1% of IC K+ to or from the EC would cause a ~50% change in SK. Indeed, a good steak meal could potentially double SK, if there were no mechanisms to modulate extrarenal K+ distribution acutely. The important mechanisms in this context are hormonal (insulin, beta-adrenergic agonists – adrenaline – and the mineralocorticoid aldosterone) and promote the rapid transfer of K+ from EC to IC via the ubiquitous ‘sodium’ (Na+/K+-ATPase) pump, and mainly into skeletal muscle.

At first sight, K+ handling by the kidney may seem a little odd, in that the proximal part of the nephron (including the loop of Henle) reabsorbs almost all the filtered K+ (~90%). The distal part secretes (primarily via the principal cell apical ROMK K+ channel and flow-dependent/activated intercalated cell apical BK K+ channel), but can also reabsorb K+ (in part via the intercalated cell H+/K+-ATPase and depending on dietary intake), and it is this segment that determines the final urine content of K+. Thus, under normal or high dietary intake, the process of distal K+ secretion accounts for most of the urinary K+ excretion, and it is this segment that responds to stimuli that can modulate K+ excretion: flow rate, lumen-negative transepithelial potential difference (depending on Na+ reabsorption), aldosterone and other factors that can affect them.

In approaching a clinical presentation of hypo- (or hyper-) kalemia, and once an extrarenal cause has been excluded (urine K+ excretion <20 mmol/day), it is sufficient to think in terms of situations that: (1) alter the delivery of Na+ to the K+ secreting distal nephron site; (2) alter the mineralocorticoid status; or (3) directly affect (damage) distal nephron (collecting duct) function. I will try to illustrate how to apply some of these physiological principles in presenting and discussing some relevant clinical examples.

References

European Uremic Toxin

Shedding a new light
The implication of microRNAs in chronic kidney disease

Development of disease is often due to the deregulation of a gene program controlled at the post-transcriptional level by microRNAs (miRNAs). miRNAs control mRNA stability or translational repression via base pairing with regions in the 3’ untranslated region. They are innovative biomarkers, and have potential as groundbreaking drugs.

We have shown that miR-126 and miR-223 are implicated in chronic kidney disease (CKD) and are associated with vessel damage, such as vascular calcification and atherosclerosis. miR-223 is increased in vitro in vascular smooth muscle cells subject ed to uremic toxins and also in vivo in a murine model of CKD.[1] miR-126 and miR-223 levels have been found to be deregulated in murine and human serum in the course of experimental CKD and in human diabetic patients.[2] We have previously demonstrated a role for miR-223 in monocyte differentiation into osteoclast in the context of chronic kidney disease-mineral and bone disorder.[3]

To follow these experiments, we decided to use a multi-omics approach to study the way in which miR-223 exerts its gene regulatory function in a monocyte/macrophage cell line, able to differentiate into either macrophages or osteoclasts. Transcriptomics and proteomics experiments evidenced changes linked predominantly to bone remodeling, cell death, histone acetylation, RNA biology and metabolism. The most important discriminant metabolites found using metabolomics were linked to metabolism and cell death, indicating that miR-223 may affect the apoptotic and proliferative state of monocytes. This exploratory study provides a base of knowledge to better understand the way miR-223 affects gene regulation and could be used to identify key components in macrophage differentiation and osteoastoclastogenesis involved in the immune response and in calcification processes related to CKD.

We also studied miRNA association with clinical outcomes. We measured the expression of serum miR-126 and miR-223 levels in a large cohort. We evaluated their link with all-cause mortality and cardiovascular and renal events over a six-year follow-up period. The preliminary results of this ongoing study will be presented during the meeting. Taken together, our findings could be of interest to both researchers and clinicians working in the field, since they might shed new light on the molecular mechanisms involved in CKD.

References
01. Biochim Biophys Acta 2014;1842:88–98
02. Biochim Biophys Acta 2017;1863:337–345
03. Biochim Biophys Acta 2015;1852(10 Pt A): 2202–2212
Gout, the most prevalent inflammatory arthritis worldwide, is characterized by deposition of monosodium urate crystals in joints as a result of chronic hyperuricemia. It has long been known that the kidney is responsible for more than 70% of urate excretion, and that hyperuricemia in gout is primarily the result of relative underexcretion of urate by the kidney.

Treatment of gouty arthritis requires both management of inflammation and management of hyperuricemia. Management of inflammation is most important during acute attacks when urate crystal deposition triggers an inflammatory response; however, if gouty arthritis progresses to an advanced stage, continuous anti-inflammatory therapy may be necessary. To control the chronic hyperuricemia, long-term urate-lowering therapy is necessary to maintain serum uric acid levels below their solubility limit.

Patients with gout typically have multiple comorbid conditions (chronic kidney disease [CKD], obesity, hypertension, type 2 diabetes, dyslipidemias, cardiac diseases, stroke and peripheral arterial disease). Hence, patients with gout also frequently harbor multiple contraindications to the drugs available for gout management; and many patients with gout are prescribed medications for their gout despite contraindications to the agents in question. Additionally, drugs targeting comorbidities may affect uricemia. Nonsteroidal anti-inflammatory drugs and colchicine are often not considered appropriate in patients with CKD. Glucocorticoids may be an effective alternative in this population; however, these agents can also cause serious side effects. Allopurinol can be used for the prophylactic management of chronic hyperuricemia in patients with CKD, but the recommended lower dosage may limit its efficacy and serious. Febuxostat and pegloticase are other treatment options for chronic urate-lowering prophylaxis; however, the safety of these drugs in patients with advanced CKD remains to be established. Uricosurics have lower efficacy in patients with CKD. To conclude, CKD is associated with increased prevalence of gout, which may be hard to treat in this population.

**Common, but hard to treat** The conundrum of treating gout in patients with chronic kidney disease

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**Molecular modifications of proteins and peptides in CKD**

**JOACHIM JANKOWSKI**

Hanover, Germany

**Systems medicine: opportunities in CKD**

**HARALD MIESCHAK**

Hanover, Germany

Gout, the most prevalent inflammatory arthritis worldwide, is characterized by deposition of monosodium urate crystals in joints as a result of chronic hyperuricemia. It has long been known that the kidney is responsible for more than 70% of urate excretion, and that hyperuricemia in gout is primarily the result of relative underexcretion of urate by the kidney.

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**Can we stop immunosuppression in autoimmune diseases?**

**DAVID JAYNE**

Cambridge, United Kingdom
A new approach to hyperphosphatemia? Prospects for inhibitors of active intestinal phosphate transport

Hyperphosphatemia represents one among several modifiable risk factors in chronic kidney disease (CKD), and the avoidance of hyperphosphatemia is a well-established goal. In CKD, hyperphosphatemia may contribute to the development of vascular calcification, cardiovascular events and increased mortality risk, either directly or indirectly via the induction of various endocrine and metabolic abnormalities.

A recent approach that blocks intestinal phosphate absorption mediated by sodium-dependent phosphate co-transporter type 2b (NPT-IIb) using either already available drugs, or developing novel inhibitors, holds promise. (Figure 1). Currently available drugs include nicotinamide and nicotinic acid, also called niacin, which is transformed to nicotinamide in the body. Of note, nicotinic acid and nicotinamide have different receptors and mechanisms of action.

Several clinical studies have shown that the administration of niacin or nicotinamide reduced hyperphosphatemia in dialysis patients, and with a lower pill burden. However, the majority of these studies were limited by short treatment periods, small sample size, and uncontrolled study design. Recently, a novel and specific small molecule, NPT-2b blocker ASP3325, has been used for the first time in humans. In a phase 1b study in patients with CKD stage 5D, ASP3325 administered three times daily for two weeks before or after a meal did not reduce elevated serum phosphate levels [1]. Therefore, the usefulness of inhibiting active intestinal phosphate transport by specific oral NPT-2b blockers for the treatment of hyperphosphatemia in patients with CKD remains uncertain. This also poses the question of the mechanism by which niacin or nicotinamide reduces hyperphosphatemia in these patients, since these compounds are thought to inhibit same transporter and in addition other phosphate transporters of the body, after their absorption from the gut. Side effects of niacin and nicotinamide are also an important issue. Niacin, but not nicotinamide, causes flushing due to stimulation of prostaglandin D2 and E2 secretion by subcutaneous Langerhans cells via the G-protein-coupled receptor (GPCR) 109A niacin receptor. Nicotinamide was found to induce thrombocytopenia in several studies in which nicotinamide was administered to CKD stage 5D patients. The nicotinamide metabolite 3PY is one of the inhibitors of poly(ADP-ribose) polymerase (PARP)-1 activity, and inhibitors of PARP have been shown to frequently induce hematological disorders in cancer patients, including thrombocytopenia, in a dose-dependent manner. Serum 3PY levels are increased in CKD patients not yet on dialysis and rise further in those on dialysis receiving nicotinamide treatment.

To conclude, the results of trials with oral inhibitors of active intestinal phosphate transport do not support the use of niacin or nicotinamide alone in the control of serum phosphate in CKD. It remains to be seen whether low-dose nicotinamide treatment, such as the ones used in the ongoing trials COMBINE or NOMPAS, will show clinically meaningful efficacy together with acceptable side effects. These trials examine the effect of nicotinamide as add-on therapy to classical phosphate binders in patients with moderate to severe CKD and dialysis patients, respectively. Their results will be presented at ERA-EDTA 2018.

References


CME 13 – CKD-MBD
Emerging insights in CKD-MBD
Thursday, 12.45–16.00, Hall A2
In chronic kidney disease (CKD) patients, the primary cause of mortality is cardiovascular disease, induced mainly by vascular calcification (VC). Pathogenesis of VC is multifactorial and incompletely understood. CKD patients are at risk of VC because of multiple risk factors. High phosphate (P) levels are associated with a high risk of VC and cardiovascular disease in both the general population and CKD patients. It has been clearly demonstrated that high P induces osteoblastic differentiation in vascular smooth muscle cells (VSMCs). Beside high P, other factors potentially causing this phenotypical change include high total body burden of calcium (Ca) and P, low levels of circulating and locally produced inhibitors, impaired renal excretion and CKD-MBD (Mineral Bone Disorder) treatments.

Commonly, treatment of hyperphosphatemia necessitates a multimodal approach: dialysis, prescription of P binders, and dietary restriction (consuming food with low P content, balancing sufficient protein intake and restricting P intake, and counteracting ‘hidden’ phosphate due to insufficient labeling of processed food). Factors influencing choice of P binder may include age, gender, diabetes, low bone turnover, vascular and/or valvular calcification and inflammation. Recently, in advanced CKD, calcium-free P binders and calcimimetics have been recommended for the treatment of hyperphosphatemia and secondary hyperparathyroidism, with the aim of delaying the progression of VC.

The scientific community has made great efforts in recent years to investigate and elucidate the mechanisms of high phosphate (Pi)-induced VC. The most common approach in vitro is to study the effect of different molecules on prevention of VC, through aspects such as calcium deposition, VSMCs osteoblastic trans-differentiation, apoptosis, elastolysis, matrix degradation and autophagy. The interest in the action of iron on calcification is supported by the recent use in the clinic of this molecule. In fact, two new Ca-free, iron-based P binders are now available to treat hyperphosphatemia in CKD, namely iron citrate (Fe) and sucroferric oxyhydroxide. In experimental models of VC, we studied the direct effect of Fe on the progression of calcification in established Pi calcified VSMCs. We investigated apoptosis and autophagy in order to elucidate potential pathogenic mechanisms.

In compliance with EBAC guidelines, all speakers/Chairpersons participating in this programme have disclosed or indicated potential conflicts of interest which might cause a bias in the presentations. The Organising Committee/Course Director is responsible for ensuring that all potential conflicts of interest relevant to the event are declared to the audience prior to the CME activities.
CKD-MBD phenotypes and mortality risk
The context of abnormal mineral bone disorder values is important

It is well established that patients with dialysis-dependent chronic kidney disease (CKD) face an increased risk of mortality. Kidney transplantation is currently accepted as the optimal treatment modality. For those who remain on dialysis, their mortality risk is targeted by optimizing dialysis schedules, promoting healthy lifestyle and additional pharmacotherapy.

A large proportion of drugs aim to optimize biochemical parameters of CKD-mineral bone disorders (CKD-MBD). This approach is logical because serum concentrations of calcium, phosphate and PTH are each associated with mortality risks and are modifiable. The recently updated KDIGO guideline on CKD-MBD defines ranges of concentrations of these biomarkers, outside which treatment should be initiated. For two clinically important aspects, little guidance could be provided, because of the absence of data on which recommendations could be based. The first area of uncertainty is the suggestion to consider the three biomarkers together, and the second is the overall absence of treatment goals.

The statement that biomarkers should be considered together is based on the assumption that the risk associated with a given concentration of, for instance, serum phosphate may be modified by the current concentration of calcium or PTH. Indeed previous analyses of large cohorts do suggest this is the case.[1] However, this has not so far changed clinical practice, where the incentive is to treat the concentration of an individual biomarker out of the context of a CKD-MBD profile (or an even broader context) or phenotype. Restoring ‘normality’ or achieving values within target range are considered as valid treatment goals, but achieving more beneficial phenotypes is not.

It is important to realize that current target ranges of MBD are set on the basis of epidemiological techniques that aim to decipher the etiology of an individual factor while correcting for other factors. This hampers definition of phenotypes based on categories with margins set by these previous studies. Moreover, the approach to definition of categories based on the ‘optimal ranges’ precludes making distinctions in risk between high and very high concentrations of a certain biomarker.

However, a logical first step to explore the concept of clinically relevant CKD-MBD phenotypes was to study the impact on risk of being within target range for all, a few, or none of the traditional treatment goals for calcium, phosphate and PTH.[2] This study, by Danese and co-workers, clearly indicated that clinically relevant CKD-MBD does indeed exist, because patients with at least two parameters out of range are at higher risk of clinical events. Analysis of a greater variety of MBD phenotypes by Block and co-workers confirmed that the MBD context of a biochemical abnormality is very relevant.[1]

The CKD-MBD working group of the ERA-EDTA is currently analyzing the EuroDOPPS dataset to move this concept forward. In this analysis, CKD-MBD phenotypes categories are not constrained by previously set target ranges, take into account the potential importance of extreme values for both phosphate and PTH, and are based on European patients. Preliminary analysis suggests that the context of abnormal values of MBD parameters is indeed highly important in which the (unadjusted) hazard rate for mortality of phosphate concentrations is dependent on current PTH concentrations. Additional analyses are ongoing with the aim of establishing CKD-MBD derived risk of a wide range of phenotypes. The ultimate goal is to test the hypothesis that a change to a phenotype with a lower risk will actually improve clinical outcome for these patients.

Central to chronic kidney disease (CKD) care is the active involvement of patients in treatment management across all G4+ stages. Most renal services provide predialysis education and supplementary patient booklets, to enable shared decision making about care plans. Yet, patients report the information provided to be both overwhelming and not sufficient to support their treatment decisions.[1]

This CME session provides an overview of how decision sciences can be applied to help health providers think differently about enabling people’s treatment decision making. Decision science theory and evidence provide insights into how people make decisions, and the information that can boost or bias people’s judgments and choices. The session focuses on research and practice carried out over the last 10 years investigating patient experiences of making dialysis decisions, providing insights into people’s judgments and choices, and the use of patient decision aids by renal practitioners to supplement PDE.[2]

References

Figure 1: Decision Map of Treatment Options as CKD Worsens (from Dialysis: Making the right choices for you. The Dialysis Decision Aid Booklet. Kidney Research UK 2017[4] with Permission from Kidney Research UK.)

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What’s new in tuberous sclerosis? mTOR inhibition is now an important option for renal angiomiolipomas

Tuberous sclerosis (TSC) in adulthood used to be more of a urological than a nephrological disease, as surgery or embolization was the only available treatment for renal angiomyolipomas (AML). Since medical therapy with mTOR inhibitors has become available, nephrologists have become more involved and may act as disease coordinators in adulthood. Neurologists take the lead for this disease in childhood, but in adulthood the renal lesions confer the highest morbidity.

Renal involvement includes cysts and AML. While cysts usually cause no clinical problems, except for the contiguous gene syndrome TSC/PKD1 (where children are affected by a Tuberous sclerosis (TSC) in adulthood used AML. mTOR inhibitors show a quick effect by now an important option for mTOR inhibition is sclerosis?

When an AML bleeds, embolization is the procedure of choice. Usually, AML are diagnosed as an incidental finding during follow-up of TSC patients. According to these findings, it could be hypothesized that blockage of the renin-angiotensin-aldosterone system (RAAS) may play a positive role in TSC-related AML.

The main risk of AML is life-threatening bleeding. The chance of hemorrhage correlates with the size of the AML and its rate of growth. Usually, AML are diagnosed as an incidental finding during follow-up of TSC patients. However, these patients may present with flank pain, palpable mass or hematuria. When an AML bleeds, embolization is the proposed first-line treatment, according to recent recommendations, followed by a seven-day course of steroids and, if this is not available, kidney-sparing surgery.

However, in the case of asymptomatic AML larger than 3 cm in diameter, the first option, according to the most recent guidelines, is treatment with mTOR inhibitors. Nowadays, we have long-term experience thanks to the EXIST-2 trial with everolimus in TSC related AML. mTOR inhibitors show a quick effect by reducing AML volume and stabilizing volume after two to three years. No patient under treatment with mTOR inhibitors has suffered any AML bleeding. Although the efficacy of the drug is remarkable, it has some side effects that will need further follow-up as it is a lifelong treatment. Some of these side effects may have an impact on renal function such as the increase in microalbuminuria. There is controversy about the impact of mTOR inhibitors on renal function, some authors supporting a beneficial effect and even suggesting early treatment before AML reach 3 cm. In any event, in the EXIST-2 trial and its extension there was no unexpected deterioration in renal function.

Interestingly, angiogenic biomarkers such as VEGF-D and collagen type IV, are increased at baseline in patients with TSC-related AML and significantly decreased compared to controls in treated patients. This supports the hypothesis that everolimus may, at least partially, act through an anti-angiogenic mechanism.

mTOR play a seminal role in TSC as shown by their effect on several manifestations of the disease. They improve subependimal giant cell astrocytomas (SEGA), pulmonary lymphangioleiomyomatosis, facial angiofibromas, epilepsy and AML. The European Medical Agency has granted approval for the use of everolimus for SEGA, AML and refractory epilepsy.

Figure 1: CT scan of a patient with TSC and enroaching AML in both kidneys © Torra

The clinical symptoms of hypophosphatemic rickets include short height, bone deformities and weakening of muscle strength. X-rays can reveal Looser-Milkaman’s zones and fatty fractures. The measurement of biochemical parameters is important to confirm the diagnosis, and include serum concentrations of phosphate, calcium, 25 OH vitamin D, calcitriol, bone alkaline phosphatase and bone markers, and PTH and FGF23. Bone histology is not necessary to confirm the diagnosis (it shows undermineralized bone and a decrease in bone formation rate). Genetic analyses can identify the gene involved.

In children, the goals of treatment are to improve growth, correct bone deformities, reduce bone pain, prevent bone fractures and – when affected as in XLH patients – to facilitate bone mineralization. The aim of treatment is to improve plasma phosphate concentration using active vitamin D metabolites and oral phosphate salts. Calcitriol or growth hormone injections can also be used. The efficacy of treatment is based on clinical data, height, weight, leg bowing and biochemical measurements; these include alkaline phosphatases, PTH, calcium, creatinine in blood, and also phosphaturia and calcitriol to reduce the risks of nephro lithiasis and hyperparathyroidism. New treatments are under evaluation that block anti-FGF23 antibodies. Tooth abscesses require specific treatments. Corrective surgery is indicated when skeletal deformities compromise function and are unlikely to improve with medical treatment.

In adults, the indication for treatment depends on the symptoms. Hypophosphatemia alone is not sufficient to initiate or reinitiate a treatment. Treatment should be started when patients complain of pain, present with fractures or very low bone mineral density (< −2.5 score), or when their mobility is impaired. Treatment is based, as in children, on the use of active vitamin D metabolites and oral phosphate salts.
the association´s new corporate identity

New colors, fresh style ERA-EDTA´s Executive Manager about the association´s new corporate identity

Many nephrologists may have noticed you have introduced a brand new logo. Why was there a need for change?

We live in very rapidly changing times, just think of how differently the “dreamers” communicate with each other compared to their parents. ERA-EDTA is one of the most important Associations in Nephrology worldwide and has a rich and important history, however after so many years since its foundation it needed renovation so as to present itself in a simple but clear way with a new logo that is meant to be more actual, impactful and immediately recognizable. It has not been simple to grasp this concept of change after all these years: change is something that can cause distrust and some obstacles had to be overcome. However, most of the merit of this choice must be given to the current ERA-EDTA Council that had the courage to make the change, but that also recognized the difference between technical issues (such as marketing for example) and scientific/educational aspects. I truly hope to be able to prove them right for the trust that they have given me through concrete results and that our members will identify themselves in this new logo and be honored to be part of an Association that is a leader in European Nephrology.

What went into the thought process for the new logo?

The process started from a mix of things, in particular, from the members themselves: it was clear that our way of communicating all the various activities of the Association was not done in a “standardized” way and even some of our core activities were not perceived as being ours. A lot of research was done, including checking out what other major Associations were doing. It was important to keep the name of the Association (which was very clear from a recent survey done among the members themselves), and to invest on this, thus being able to be recognized without having to explain our acronym; it was also important to include a kidney symbol in the logo so as to highlight our field of interest, finally, refresh it with bright colors. This process of change has helped to “put order” in our way of communicating, to optimize our staff resources and to prepare our Association towards the future challenges making sure that our members identify themselves with who we are and what we do.

What about the design process – how long did it take to finish the job?

It was a very long task, it took many months, particularly, from the members themselves and, as mentioned above, without the support of the entire Council and, in particular of my current President, Prof. Carmine Zocca. When will the job be finished? Well, such an important initiative is an on-going job, at least at the beginning, thus I consider it to be still in progress.

There has been a quite radical re-design of the association´s corporate identity (CI). What is the “logic” behind the new CI?

Yes, you have pinpointed the main matters! My staff and I are involved in re-evaluating, from a branding point of view, a series of initiatives, projects and communication methods the results of which will only be fully seen in the medium-long term. Some guidelines of this can already be seen here at the Congress, for example, the choice of a “color code” system to identify the various core activities of the Association: Education, Research, Association and Institutional. The aim is that of giving focused communication.

What image is transported via the new CI? Will the new design set ERA-EDTA apart?

The new image was launched just a few months ago and the Congress will be a bit of a first test: I expect, and hope, to receive some constructive criticisms that will help us to even more improve our image in general. I however am totally convinced that this is a big step in the right direction but would be a fool if I thought of seeing the results immediately, as mentioned, this is a long term project.

What have been the reactions of the ERA-EDTA members, other medical associations and your staff so far?

Well… overall, quite good. I’ve received positive feed-back, but also found some difficulties: even you were a bit sceptical of the change! However I think that this is absolutely normal and am very hopeful that it will be a success, especially thanks to the positive energy that everybody, especially the staff, has shown in view of this renovation. I’d actually like to take advantage of this interview to thank, a part from the ERA-EDTA Council members, all the staff for their great commitment as well as their patience!
Onco-nephrology: a new subspecialty
The nephrologic management of renal and urothelial cancer

Onco-nephrology is a new and rapidly evolving subspecialty that focuses on the complex relationship between the kidneys and cancer, a relationship that has been defined as ‘circular’. Kidney and urothelial cancers are among the areas where nephrologists and oncologists should work closely together in future in order to provide cutting-edge care for patients afflicted with both cancer and kidney diseases.

Kidney cancer remains the only malignancy where surgery (either total or partial nephrectomy) is indicated even in the presence of metastatic disease. It is now quite clear that patients who have undergone nephrectomy are at increased risk of developing both acute kidney injury (AKI), as well as de novo chronic kidney disease (CKD), and worsening of pre-existing CKD, especially in the presence of certain comorbidities. Furthermore, the presence of CKD increases the risk of developing all types (not only renal) of oncological treatment-related adverse events. Thus, while the urologist is primarily involved, close follow-up by both the nephrologist and oncologist is warranted for all nephrectomized patients before and after surgery, as well as during oncological treatment, if any.

Urothelial cancer is a family of different neoplasms characterized by an extremely high incidence of kidney impairment throughout its whole natural history; furthermore, surgical and medical treatments may often worsen kidney function, or cause renal adverse events. In this setting, nephrologists could help to deal with episodes of AKI, or of a worsening of CKD due to obstruction/infections – episodes that are quite common in patients with non-muscle-invasive tumors undergoing several transurethral resections. In muscle-invasive neoplasms, an adequate and timely nephrological evaluation could help to reduce the number of patients unsuitable for cisplatin-based neo-adjuvant (or adjuvant) chemotherapy, or of those who cannot complete the scheduled treatment due to deterioration in their kidney function.

In patients undergoing nephrectomy (in the case of upper urinary tract neoplasms) or cystectomy (in the case of bladder cancers), deterioration of renal function is also extremely frequent. Post-operative hydronephrosis, pyelonephritis and uretero-enteric stricture indeed represent other potentially modifiable factors associated with a decrease in kidney function. Finally, in the metastatic setting, the nephrological management of renal toxicities from systemic therapies would also be increasingly important.

The need for the involvement of the nephrologist in the complex management of patients affected by these two malignancies is, in our opinion, highly warranted – once again, advocating for a truly comprehensive multidisciplinary management of these patients.

References


End-of-life perspectives in hemodialysis
We need to integrate palliative care into the nephrology clinic

Patients with end-stage renal disease (ESRD) on dialysis, or with conservative care without dialysis, suffer from a variety of clinical and subjective symptoms, such as fatigue, pruritus, pain, sleep disturbance, nausea, muscle cramp, restless legs, anorexia, depression and dyspnea. Many patients are old and have a multiplicity of comorbidities, such as diabetes, cardiac disease, cerebrovascular disease and peripheral vascular disease, which add to the complexity and burden of their symptoms.

Comorbidities also add to reduced life expectancy and high mortality rates: about 15–20% annually in patients on hemodialysis. Different trajectories of death with ESRD have been described; e.g. sudden death with little warning, terminal illness with rapid decline, organ failure with episodes of acute deterioration, and for the very old and persons with dementia, a gradual decline with frailty. Dialysis withdrawal precedes about 15% of deaths and the average time of survival after dialysis withdrawal is eight days.

It has been questioned whether older patients with ESRD and multiple comorbidities are likely to benefit from start of renal replacement therapy (RRT). Patients with an anticipated poor prognosis may choose to forgo dialysis and decide to be treated conservatively instead. Ideally, conservative management should entail ongoing professional care with full medical treatment, including control of fluid and electrolyte balance, anemia correction and provision of appropriate palliative and end-of-life care. Shared decision making with the patient and relatives has been recommended to enable a joint decision on RRT by considering potential benefits and harms of all treatment options and the patient’s preferences.

It is problematic to predict end-of-life trajectories for patients with ESRD, but mortality rates imply that many old and frail hemodialysis patients are living their last year of life. In a chronic, progressive disease, it is sometimes difficult to know when end of life begins. Hence, these patients need to discuss prognosis to be able to make decisions and plan for end of life according to their personal values.

The World Health Organization emphasizes the need for palliative care, comprising symptom management, teamwork, communication, relationships, and family support aimed at preventing and relieving suffering and enhancing the quality of life of patients with a life-threatening illness, such as in ESRD. However, in the hemodialysis unit, where most focus is on handling advanced medical technology and maintaining life, end-of-life or palliative care may be neglected or overlooked.

Withholding or initiating withdrawal from dialysis has long since been the focus of palliative care for patients with ESRD. However, the aging patient population with their complex symptoms and comorbidities has raised awareness of the need to integrate the palliative care approach earlier in outpatient nephrology care and for a longer time. Most patients want discussions about their prognosis, and earlier discussions may help them to plan for their future. Implementation of the philosophy of palliative care in the hemodialysis unit, with active care for the whole person, has also been put forward as many patients suffer from continuous deterioration.

References


In a European survey, most nephrologists reported that palliative care had not been part of their core curriculum or recent medical education. Hence, both primary palliative care training of nephrologists and renal nurses, and collaboration with palliative care specialists should be emphasized in future renal care.

There is a need for further comprehensive studies describing the care situation and key components of palliative care activities for this group of patients when close to death.
Do we still need calcineurin inhibitors in 2018?

Kidney transplantation has been performed worldwide since the 1960s with maintenance immunosuppressive drugs such as steroids and azathioprine. Cyclosporin (CsA) resulted in a 15% improvement in overall graft survival when tested against azathioprine in a randomized controlled trial (RCT). CsA was then adopted worldwide as the cornerstone immunosuppressive drug after some months (conversion), or to stop CNIs from an established combination of drugs (withdrawal).

The overall results of these approaches have been summarized in a meta-analysis. Conversion or withdrawal from CNIs to mTOR (sirolimus [SRL] or everolimus) was associated with improvement in renal function (+7 ml/min), but also with an increased risk of biopsy-proven acute rejection (BPAR) (RR, 1.7). Furthermore, another meta-analysis of RCTs comparing SRL with mainly CNIs found an increased risk of death (HR, 1.4) in the SRL group. Therefore these strategies have been largely abandoned today. CNI withdrawal plus mycophenolate (MPA) versus maintenance on CNI again resulted in improved kidney function (+7 ml/min), but was also associated with a significantly increased risk of BPAR (RR 3.2), and this strategy is also not widely used.

A new class of agents, namely co-stimulation blockers, has been investigated during the last decade for their ability to enable CNI avoidance. The most studied agent is belatacept, a fusion protein composed of the Fc fragment of human IgG1 linked to the extra-cellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). It selectively inhibits T-cell activation through costimulation blockade. Substituting CsA for belatacept led to an increased risk of first-year BPAR (20% versus 7% in the CsA group), but resulted at seven years in better overall graft and patient survival (87% vs 78%, p = 0.02). Furthermore, kidney transplant function was significantly better with belatacept compared to CsA (eGFR: 70 vs 45 ml/min). Fewer HLA donor-specific antibodies were produced in the belatacept arms. Also of note was better control of the metabolic profile, likely contributing to improved patient survival. Thus belatacept is the first drug since CsA to improve overall graft survival. It was approved by both the FDA and the EMEA in 2011. Disappointingly, use of belatacept remains minimal in both the US and EU. Its cost (1,000 €/m vs 100 € for CNIs) remains prohibitive for many countries. Furthermore, the lack of good, adequately powered studies comparing belatacept to tacrolimus, the most widely used CNI today, remains a caveat for many transplant physicians. Nevertheless, the belatacept trials are proofs-of-concept that we will witness the sunset of CNIs within the next decade. Whether the costimulation-blocker that will emerge in the clinic will be belatacept, or a CD40 or CD28 blocker, remains to be seen.

References

A new option for dietary phosphate control
The New Nordic Renal Diet and chronic kidney disease

Chronic kidney disease (CKD) causes severe disturbances in phosphate homeostasis, and observational studies link hyperphosphatemia and elevated levels of fibroblast growth factor (FGF23) to the increased cardiovascular morbidity and mortality seen in CKD. Phosphate binders are prescribed when hyperphosphatemia is manifest, typically at CKD stage 4–5, but both FGF23 and parathyroid hormone are already elevated at CKD stage 2–3. This indicates an unmet need to develop safe and sustainable therapeutic approaches in the early CKD stages to prevent disturbances in phosphate homeostasis, in order to postpone or even prevent the vascular calcifications and left ventricular hypertrophy found in the majority of end-stage renal disease (ESRD) patients.

Dietary phosphorus exposure and absorption are modifiable risk factors. However, studies of dietary interventions, often in combination with phosphate binders, to reduce plasma phosphate and FGF23 in patients with moderate CKD have shown conflicting results. Some demonstrated a positive effect, especially on FGF23, while others have failed to show any difference.

Dietary restrictions are widely recommended, but difficult for patients to follow. Changing the eating habits of a population on a long-term basis presents a major challenge. However, this change is needed due to the Western diet containing a considerable amount of meat-based protein that is typically high in phosphorus content of the New Nordic Diet and did not find it suitable for the CKD population in its present form.

The beneficial effects of healthy-eating habits for cardiovascular morbidity and mortality have been demonstrated by two widely recommended food-based dietary patterns: the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet. Both dietary interventions, often in combination with phosphate binders, to reduce plasma phosphate and FGF23 in patients with moderate CKD have shown conflicting results. A recent Danish initiative to develop palatable, healthy and sustainable dietary recommendations favoring organically produced food items, fruits, vegetables, whole grains and fish from the Nordic region – termed the New Nordic Diet – has been tested in different population groups with promising results regarding cardiovascular risk profile. The diet is very similar to the Mediterranean diet, but substitutes, for example, rapeseed oil for olive oil, ramsoms or wild garlic for garlic, etc. We have previously tested the phosphorus content of the New Nordic Diet and did not find it suitable for the CKD population in its present form.

A modification of the New Nordic Diet into a New Nordic Renal Diet to suit the needs and preferences of a Danish CKD stage 3–4 population regarding important parameters of phosphorus homeostasis has been tested. The study demonstrates that lowering dietary phosphorus intake by 650mg/day, without pharmacological intervention, is sufficient to show a positive result on both FGF23 and phosphorus urine excretion in moderate CKD patients.

S 4.9 CKD—a new therapeutic approaches
Friday, 08:00—09.30, Hall A2

YouTube
View the ERA-EDTA 2018 Broadcast on the YouTube playlist here.
Diabetic Kidney Disease: Exploring mechanisms and outcomes of SGLT2 inhibition

What's going on in Copenhagen?

Donkey Republic
Donkey Republic is the easiest way to rent a bike in Copenhagen. Find your bike nearby and unlock with the Donkey Republic app. No internet connection is required, no docking stations, no cash, no ID cards. Get a 10% Discount using the code "ERAEDTA10". www.donkey.bikes/cities/bike-rental-copenhagen

Experience colourful Christiania
Freetown Christiania is a green and car-free neighbourhood in Copenhagen, best known for its autonomous inhabitants' different way of life. It was established in 1971 by a group of hippies who occupied some abandoned military barracks on the site and developed their own set of society rules, completely independent of the Danish government.

The Copenhagen Opera House
For music and architecture lovers: The Copenhagen Opera House was designed by Danish architect Henning Larsen, and a number of Danish artists have contributed to the decor, among them Per Kirkeby who has created four bronze reliefs, and Danish-Icelandic artist Olafur Eliasson who has contributed the three light sculptures for the foyer.

Beautiful illuminations at the Tivoli Lake
May 24th, 22.45
The Tivoli Illuminations are a fantastic lighting show that creates a dream universe with colors, music, lasers, fire, smoke and water. Tivoli Illuminations are best seen from the bridge above the Tivoli Lake or in the area in front of the attraction Vertigo. www.tivoligardens.com

Summer Classical/Tivoli Concert Hall
May 24th, 19.30
This concert is one of 34 classical concerts during the summer season presenting carefully chosen local semi-professional orchestras or upcoming musicians from the region's conservatories. Tonight: Igor Stravinsky’s "The History of a Soldier" as well as "Contrasts" by Béla Bartók.

Nyhavn
Especially during summer, Nyhavn is the perfect place to end a long day. With a cold one on the quay like the locals, or at one of the many restaurants. Originally, Nyhavn was a busy commercial port where ships from all over the world would dock. Today restaurants dominate the old port. Enjoy the relaxed atmosphere by the canal, jazz music and great food.
Cyclophosphamide: still a role in membranous nephropathy? It remains an important drug, especially for patients at highest risk of disease progression

Primary membranous nephropathy (pMN) is the most common cause of nephrotic syndrome in Caucasian adults. In the past decade, tremendous progress has been made in unraveling its pathogenesis. It is now proven that pMN is a renal-limited autoimmune disease, characterized by the presence of antibodies against podocytic antigens.

The predominant antigen is the Phospholipase A2 receptor (PLA2R), a podocytic membrane protein. Serum antibodies against PLA2R can be detected in approximately 70% of patients with pMN. The disease course in patients with pMN is quite variable: 40–50% of patients will develop a spontaneous partial or complete remission within three to five years after onset of disease. Even so, without appropriate therapy, approximately 50% of patients will have progressive disease and develop end-stage renal disease (ESRD).

Alykating agents such as chlorambucil and cyclophosphamide have been used in nephrology for more than 50 years. The efficacy of these agents in improving outcome in patients with pMN was proven in randomized controlled trials (RCT). The first RCT was published almost three decades ago, and introduced the ‘Ponticelli’ regimen, a combination of chlorambucil and prednisone. In later studies, cyclophosphamide was used, and was as effective and somewhat less toxic.

Although the efficacy of cyclophosphamide is undisputed, the drug is associated with severe side effects, both short-term (infections, infertility) and long-term (malignancies). The introduction of other immunosuppressive drugs into the clinic brought hope and expectations that they could replace cyclophosphamide in the treatment of pMN. Indeed, cohort studies and small-sized trials have shown that mycophenolate mofetil, ACTH, calcineurin inhibitors and rituximab can induce remissions of proteinuria. Unfortunately, data on hard renal endpoints such as ESRD or doubling of serum creatinine are lacking. Moreover, relapse rate after use of calcineurin inhibitors, mycophenolate mofetil or ACTH is quite high, which is a cause for concern since frequent relapses increase the likelihood of developing ESRD. Rituximab might be most promising in this respect, although long-term outcome data are lacking.

A recent study compared the outcome of patients with pMN treated in two centers, one preferentially using rituximab, the other using cyclophosphamide. Use of rituximab was associated with fewer serious adverse events. However, partial remission rate was higher with cyclophosphamide, which could predict better long-term renal outcome. In a pilot study evaluating immunosuppressive rate, the difference between rituximab and cyclophosphamide was confirmed. Cyclophosphamide and rituximab were equally effective in inducing an immunological remission in patients with low and moderate PLA2R antibody titers; however cyclophosphamide was more effective than rituximab in patients with high PLA2R antibody levels.

We can expect that, in the near future, treatment algorithms will use risk assessment based on PLA2R antibody levels to select the best drug for the individual patient. Although its use will decline, cyclophosphamide will remain an important drug, especially for patients with pMN at highest risk for disease progression. Studies are under way to determine if the duration of treatment with cyclophosphamide can be shortened or the dose reduced by using intravenous dosing.

IgG4-related kidney disease

Diagnosing and treating this recently recognized disorder

IgG4-related disease (IgG4-RD) is a recently recognized disorder characterized by tumefactive lesions or organ enlargement, elevated serum IgG4 and IgG levels, C3 and/or C4 hypocomplementemia, peripheral eosinophilia, antinuclear antibodies and rheumatoid factor. Ultrastructural, contrast-enhanced computerized tomography, magnetic resonance imaging, and 18F-fluorodeoxyglucose positron emission tomography/computed tomography play fundamental tools for monitoring therapeutic response and guiding intervention.

Pathological features are characterized by dense cell interstitial infiltration, predominantly composed of plasma cells and lymphocytes that can be either diffuse or multifocal. Eosinophils are frequently seen. In some cases, a dense cellular infiltrate with minimal fibrosis is observed, while other cases are characterized by a more densely cellular inflammatory lesion with expansion of interstitial fibrosis or collagen-rich, paucicellular fibrosis. Another frequent lesion is stromal fibrosis, characterized by a swirling pattern of fibrosis resembling the spokes of a car wheel with spindle cells radiating from the center. Obliterative phlebitis, a critical pathological feature of IgG4-RD, is rarely seen in IgG4-related TIN. Immunostaining of tissues typically reveals more than 10 IgG4+ plasma cells/hpf and an increased IgG4:IgG plasma cell ratio (>40%) relative to healthy tissue.

Cellular immunity, and particularly T-cells, are implicated in disease pathogenesis. In fact, CD4+ T-cells are abundant within IgG4-RD lesions, and may secrete cytokines such as IFN-γ and TGF-β that recruit and activate fibroblasts. A separate T-follicular helper cell population producing IL-4 and IL-10 might promote class-switching of IgG antibodies to IgG4 and differentiation of B cells into plasma cells. Lastly, regulatory T-cells likely play a central role in IgG4 and TGF-β production in the interstitium, thus promoting interstitial fibrosis.

Glucocorticoids represent the first line of therapy for both IgG4-RD and IgG4-RKD, but disease relapse after tapering or discontinuing treatment is very high, and long-term use of glucocorticoids is associated with various adverse events. Rituximab (RTX) is frequently used as second-line therapy, especially in refractory cases. Immunosuppressants such as azathioprine, mycophenolate mofetil, methotrexate and cyclosporine have been used as glucocorticoid-sparing agents, or in patients showing incomplete response. However, their efficacy has not been demonstrated.

We recently reported a small case series [1] in which four patients were treated with an intensified immunosuppressive protocol combining steroids, cyclophosphamide and RTX, and showed remarkable functional, histological, immunological or radiological response.

References

[1] 01. OncoTarget 0: 21337–21347, 2018
The ERA-EDTA Registry participates in a work package of the EDITH project that will address the epidemiology and costs of different treatment modalities for ESKD. One of the aims of this work package is to examine factors that influence the choice of treatment modalities made by patients and nephrologists. To this end, the EDITH kidney patient survey on treatment modality choice is currently being distributed among dialysis and kidney transplant patients in almost all European Union Member States and associated countries; the questionnaire for nephrologists will follow. The EDITH kidney patient survey is available in various languages and can be found at www.edith-project.eu.

Kidney transplantation provides the greatest longevity and highest quality of life at the lowest costs, but unfortunately remains underutilized. Hence, a significant part of the EDITH kidney patient survey focuses on the barriers and facilitators of receiving a kidney transplant from a living or deceased kidney donor in the different European countries. As a substantial group of patients with ESKD may not be suitable for a kidney transplant, the survey also investigates barriers and facilitators for particular forms of dialysis. Other parts of the survey involve the type of and satisfaction with the information provided on each modality and the extent to which patients were involved in the decision-making process. The results are expected to differ across the European countries.

The EDITH project may have an impact on the treatment choices made by patients and doctors and on health care policies, and could help improving the access to dialysis and in particular to kidney transplantation in European countries. See also www.edith-project.eu.

References

CME 3 – DESCARTES Kidney transplantation: what are the challenges and opportunities ahead? Thursday, 08.45 – 12.00, C1-M1-2

S 0.1 ERA-EDTA Registry Saturday, 11.45 – 13.15, Auditorium 15

The European EDITH project The kidney patients survey on treatment modality choice

The kidney transplantation: still a challenge: the tireless search for an effective, targeted therapy will be discussed.

The aims of this work package is to examine factors that influence the choice of treatment modalities made by patients and nephrologists. To this end, the EDITH kidney patient survey on treatment modality choice is currently being distributed among dialysis and kidney transplant patients in almost all European Union Member States and associated countries; the questionnaire for nephrologists will follow. The EDITH kidney patient survey is available in various languages and can be found at www.edith-project.eu.

In 2018 FSGS is still a puzzling disease[1]: the hanging sword of steroid responsiveness raises huge anxiety about progression toward renal failure and even more of post-transplant recurrence, particularly when dealing with children. A convincing, fully explanatory pathogenetic mechanism is still elusive, and in spite of many advances in understanding of genetic and immunologic factors, we are only at the dawn of reliable biomarkers of progression and of post-transplant recurrence.

Some answers have come from genetics: about one third of the children and young adults with FSGS harbor mutations in genes encoding for proteins of the podocyte, slit diaphragm or glomerular basement membrane. Today at least 53 mutations are known, the most prevalent on NPHS1 (nephrin), NPHS2 (podocin), and WT1. The identification of a homozygous, compound heterozygous or pathogenetic dominant mutation in these genes is a cause for great relief: these cases do usually not recur after transplant. The concern about recurrence risk is higher for recessive heterozygous and when no mutation is identified, possibly due to an immunologic or other unidentified pathogenetic factors.[2]

Immediate massive post-transplant recurrence of nephrotic syndrome has consolidat-ed the hypothesis of a pre-formed circulating podocytotoxic substance, coined ‘permeabi-lity factor’. Although very convincing in theory, no conclusive agreement has been obtained: the origin of this factor has shifted over the years from a cytokine, to a substance with affinity for galactosidase and, more recently, to the soluble receptor for urokinase-type plasminogen activator (suPAR). Expectations were high for SuPARs, followed by general disap-pointment when it was identified in advanced CKD, as well as in multiple primary or secondary glomerular diseases, inversely cor-responding to GFR.

After experiencing a complex, unresponsive, often rapidly worsening primary disease, the immediate recurrence of nephrotic syndrome after kidney transplant is one of the most frustrating and discouraging of events. Ex-treme variability of presentation and evolution of a rare disease do not allow for solid experimental approaches, and different combi-nations of drugs and apheresis techniques have been attempted. Most of the contribu-tions in the literature are small case series or case reports about different combinations of old drugs, sometime offering consistently good results, but mainly in uncontrolled and highly biased protocols.[3]

The backbone of treatment for recurrence is the removal of the putative circulating fac-tor through plasmapheresis or immunoad-sorption associated with the suppression of its production with immunosuppressive regi-mens. Nowadays, the latter is mainly with the anti-CD20 monoclonal antibody rituximab.[4] New guns, such as abatacept, belatacept, anti CD40 and olafumab were recently added to the armory with some encouraging results.

Another unsolved question is the utilization of living-related donation for patients with genetic FSGS. Here the problem is double faced: on one hand, the risk for the donor is unclear and, as described in some cases, donation may accelerate the manifestation of a latent FSGS; on the other, the recipient might be at higher risk of disease recurrence. Some ge-netic features such as the R229Q of podocin have been identified as at high risk, but no other definitive information is available for the other mutations.[5]

FSGS and its recurrence after transplant are still a challenge: the tiresome search for an effica-cious, targeted therapy will be discussed.
At the crossroads of metabolic and vascular disease

Insulin resistance is a key mediator of obesity-related vascular disease

Insulin is an anabolic hormone secreted by pancreatic beta-cells, and has a pivotal role in energy homeostasis through modulation of mainly glucose and lipid metabolism. During the postprandial period, insulin is needed for efficient entry of glucose into muscle, liver and adipose cells. Impaired fasting blood glucose is mainly related to central insulin resistance. Insulin resistance is a highly obesogenic environment with insulin resistance at the cellular level. Recent studies have identified more than 50 genomic regions associated with hyperinsulinemia – the first manifestation of increased insulin resistance – with dyslipidemic features in a large general population. Individuals with a higher genetic predisposition to insulin resistance were found to have a relative inability to expand the peripheral, subcutaneous adipose tissue compartment when exposed to caloric-dense foods. This incapacity results in the increase of ectopic fat deposition in the liver, kidney, heart, and within myocytes of skeletal muscle and other organs. In the liver, ectopic fat accumulation, mainly through increased diacylglycerol (DAG) content, leads to a sustained activation of protein kinase C. This inhibits proximal insulin signaling at the level of IRS-1 phosphorylation and results in a reduced activation of hepatic glycogen synthesis and postprandial hyperglycemia. Similarly, accumulation of DAG impairs muscle insulin signaling, whereby ingested glucose is diverted from the muscle to the liver, where it becomes a substrate for hepatic lipogenesis. Adipose tissue contributes to systemic insulin resistance mainly through release of fatty acids, glycerol and signaling adipokines that further drive hepatic lipid and glucose synthesis via substrate push.

Endothelial cells play an important role within the tissue microenvironment in establishing systemic insulin sensitivity: when the delivery of insulin to peripheral tissue is impaired due to endothelial dysfunction, this contributes to systemic insulin resistance. Thus, endothelial cells may represent a critical boundary between vascular biology and metabolism. Dysregulated endothelial function is thus not only the sequela of metabolic disease, but also a contributing factor to pathogenesis and progression of metabolic disease.

Finally, very simple solutions exist to the many deleterious effects of ectopic fat deposition and insulin resistance on the body: reduced calorie intake and exercise. Aerobic exercise improves insulin sensitivity by activating the insulin-independent glucose uptake to bypass the block in insulin signaling, eventually reestablishing normal postprandial muscle glycogen synthesis. Yet combating increased caloric intake and a sedentary lifestyle seems like a much more complicated task compared to delineating pathophysiology and mechanisms of adverse effects of insulin resistance.

References


CME 7 – DIABESTY
Insulin resistance and renal disease
Thursday, 08.45–12.00, C1-M4

CME 4 – EUADIAL
Improving outcomes for the haemodialysis patient
Thursday, 08.45–12.00, Auditorium 15

So, what does ‘improving outcomes’ actually mean?

When you look at aggregate chronic kidney disease (CKD) data you see trends and percentages, incidence and prevalence, mortality and morbidity. However, hidden in amongst this data are real people, living real lives with real problems. So I would like to challenge the traditional medical meaning of ‘improving outcomes’ from a surviving patient’s perspective with 25 years of experience.

Three things improving outcomes does not mean...

1. Treating the symptom burden with inadequate and sometimes detrimental drugs because they are cheaper.
2. Treating people with an amount of dialysis that is deemed ‘sufficient’ or ‘adequate’, mostly by people who have never experienced dialysis for themselves.
3. Patients having to put up with stress and anxiety due to poor enabling technique by professionals

Three things it does mean

1. Realizing that ‘normal life’ as most people know it changes forever when you dip below 20% GFR. Work, holidays, savings and pensions, family, relationships, the future... all suffer as a result.
2. Facilitating patients to learn about dialysis through a variety of methods. By far the most powerful is talks by expert patients willing to help others. This should be properly organized and supported by renal professionals, and should cover important aspects, such as modality choices, diet and fluid, and real life with renal failure.
3. Remembering that one size does not fit all when it comes to patients. We need your attention, we do not want to be labelled, put in a box and reduced to a statistic. What we want above all else is some semblance of normality.

In the last 25 years of my life, the best years have, without a doubt, been the last nine on single-needle nocturnal dialysis, with a treatment regimen of up to 60 hours per week. There seems to be very little knowledge and experience of nocturnal at many centers, and programs are slow to get started. Many centers are not willing to do nocturnal, are simply unaware of it, or unable to share best practice with other centers.

For me, the biggest thing that could have improved outcomes would have been someone to talk to, someone to help me understand that kidney failure is not the end of the road, rather it is a new road. It is a road that needs adequate preparation, learning and gaining of a deeper understanding of all the facts available, to enable me to make the right decisions for my unique journey.
The impact of research is difficult to define and measure. This is particularly true of research at population level, where benefits may take many years to accrue and determination of causality (and therefore the ability to attribute change to specific interventions) may be impossible. The aim of this session is to explore the public health impact of research by considering commonly used epidemiological study designs, the kinds of evidence they can produce, and how their impact may be assessed.

The World Health Organization defines epidemiology as the “study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems”. Epidemiology is therefore the core science of public health, which is concerned with improving the health of populations. This is extremely important in kidney disease, where ‘upstream’ problems such as obesity and hypertension are driving a marked increase in chronic kidney disease (CKD) prevalence in many regions.[1]

In considering public health action, it is important to consider not just those at highest risk of disease, but also the wider population. As Geoffrey Rose identified: “A large number of people at a small risk may give rise to more cases of disease than the small number who are at high risk.”[2] The role of clinicians in healthcare settings is obviously vital in conditions such as CKD, but public health impact may also be achieved through interventions that rely less on individual clinician effort and more on a societal change.

Some questions that are important for health services and policy makers may not be answerable by randomised controlled trials. Other epidemiological study designs such as cross sectional, case control and cohort studies may be more appropriate. Each has potential for public health impact through their specific design characteristics. Identifying need (and unmet need) is a key public health activity, for example, that may only be achieved by observational studies. However, traditional measures of population impact from epidemiological studies, such as population-attributable risk, while important in describing the extent to which an exposure contributes to disease in a population, have limitations in the real world. The broader public health impact of research is more complex and difficult to measure. An impact matrix developed by Cruz Rivera et al summarizes the many methodological frameworks that have been proposed to assess research impact.[3] This is helpful in describing the public health impact of research because it includes domains that reflect impact on policy makers, health systems and wider society. This will be considered in this session using CKD as an important example.

In resource-constrained environments, there is an urgent need to achieve the best value in research by reducing avoidable waste. This can be done by choosing the right research questions, conducting appropriate, well-designed studies, and promptly publishing unbiased and accessible reports of research. In doing this, epidemiological studies will continue to have an important role in influencing public health action and outcomes in kidney disease.

References

Systems medicine: opportunities in CKD
Identifying molecular mechanisms and pathways to implement personalized therapy

Chronic kidney disease (CKD) is a multifactorial disease with an unmet need for early detection and efficient therapeutics. CKD is initiated and progresses on a molecular level, followed by morphological changes at later stages. Therapeutic treatment targets molecular alterations and should ideally regress the molecular changes, and prevent onset and progression of the clinically relevant disease. The multifaceted molecular nature of CKD, together with associated co-morbidities, represent a major obstacle in disease management and in clinical trials, emphasizing the limitation of approaches targeting single causes and symptoms of the disease. As such, CKD complexity underscores the need for integrative analyses towards understanding its pathophysiology through the definition of underlying molecular causes. With advances in the field of high-resolution analytical omics technologies, a stream of data encompassing genomics, proteomics, metabolomics and pharmacology has become available. Diagnosis and treatment based on patients’ molecular profiles, initiating personalized medicine, appear to become possible. Combining omics datasets with clinical information and knowledge on pathophysiology offers insights into disease phenomena encapsulating the principles of Systems Medicine. Omics repositories, as well as disease-specific databases in the field of CKD, are essential to this approach, supporting data mining and validation of findings.

The generation of first molecular maps of CKD highlighted major pathways involved, emphasizing, however, the high variability of molecular signatures and consequently the need for large datasets. The strategy employed includes a comprehensive systems biology approach integrating omics within a CKD-relevant interactome, focusing on statistical, functional and correlation-linked data. Several studies described the construction of multi-level molecular interactomes, which helped explaining disease mechanisms, generate hypotheses and resulted in new discoveries.[1] For instance, integration of multi-omics data related to IgA Nephropathy yielded several proteins of potential therapeutic or biomarker role.[2] Similarly, systems approaches highlighted the association of inflammatory pathway Janus kinase-signal transducer and activator of transcription (JAK-STAT) with the progression of diabetic nephropathy. Consequently, JAK inhibitors tested in a phase 2 clinical trial significantly reduced albuminuria in type 2 diabetes patients.[3] A major factor involved in diabetic nephropathy is attenuation of collagen degradation, resulting in an increased collagen deposition and fibrosis. Matrix metallo- proteases, key enzymes involved in collagen homeostasis, are significantly modulated by hypoxia. At the same time, the effect of enhanced hypoxic response on collagen accumulation can be influenced by spironolactone. Based on a systematic assessment of mostly proteomics data, the hypothesis was generated that collagen degradation and fibrosis can be effectively displayed using urinary peptide biomarkers, and these could be used to guide early intervention with spironolactone to prevent onset and progression of the nephropathy. As a result, the PRIORITY trial (www.eu-priority.org) was initiated, which will, if positive, represent the first example of personalized treatment in nephropathy.

References

Improving population kidney health designs and public health impact
Epidemiological study

The impact of research is difficult to define and measure. This is particularly true of research at population level, where benefits may take many years to accrue and determination of causality (and therefore the ability to attribute change to specific interventions) may be impossible. The aim of this session is to explore the public health impact of research by considering commonly used epidemiological study designs, the kinds of evidence they can produce, and how their impact may be assessed.

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References

CME 5 – ERA-EDTA Registry
Thursday, 09.15–12.00, Hall A3

CME 9 – EUTox
Uremic toxins: sources and alterations leading to the uremic state
Thursday, 08.45–12.00, C1-M0

ERA-EDTA - Daily Congress Newspaper

55th ERA-EDTA CONGRESS COPENHAGEN DENMARK – MAY 24th – 27th 2018 – E-ISSUE 1 – PAGE 4
The use of glucocorticoids with immunosuppressive drugs has been a central pillar of therapy of immune-mediated renal diseases for over 50 years. While much is known about their effectiveness, as biomarkers we struggle to know when to withdraw glucocorticoid suppression, which we may help to elucidate the pathological role of protein modifications. However, the mass-spectrometry-based method was highly sensitive and mainly the minimization of toxicity, much less is known about the duration of therapy. This is partly due to the difficulty and cost of conducting trials over many years, and partly to the absence of reliable surrogate markers to predict which patients are at risk of relapse.

Molecular modifications of proteins and peptides in CKD

Post-translational modifications of proteins and peptides have recently gained much attention, as they are involved in the pathogenesis of cardiovascular diseases. Post-translational modifications are covalent changes of proteins or peptides that are altered either by proteolytic cleavage or by adding moieties to one or more amino acids. This enhances their complexity with respect to regulation of activity state, subcellular localization, turnover and interaction with other cellular molecules. These modifications alter dramatically physiological and pathophysiological properties of the proteins. Several post-translational modifications have been described in recent years, for example advanced glycosylation, oxidation, nitrosylation, carbamylation or acetylation.

Based on these descriptions, post-translational modifications proteins and peptides have gained attention as biomarkers and/or mediators of cardiovascular disease and chronic kidney disease. Analysis of these post-translational modifications plasma proteins in more detail are an urgent task in renal research to identify mechanisms which play a role both in the genesis and/or progression of chronic kidney disease and cardiovascular disease since proteins are constantly being exposed to different plasma and tissue components under different pathophysiological conditions like renal failure.

Recent progress in mass-spectrometry caused a dramatic increase in selectivity and sensitivity of these methods. Based on these advancements, we are now able to reliable and reproducible identify and quantify endogenous post-translational modifications of proteins. Especially matrix-assisted laser desorption/ionisation (MALDI) mass-spectrometry allows an analysis of post-translational modifications, since MALDI mass-spectrometry produces less multiply charged ions as compared to e.g. electrospray ionisation and the time for the mass-spectrometric is not limited due to time-effects. Based on this background, quite recently a comprehensive method for analysis of these post-translational modifications was established for the clinical diagnostics.

The method was established by using albumin – the most abundant plasma protein in human – isolated from chronic kidney disease patients and healthy controls by chromatographic steps. Post-translational modifications of albumin were identified by MALDI mass spectrometry after tryptic digestion by analysing mass-signal shifts of albumin peptides using pertinent mass-databases. It was demonstrated that albumin isolated from plasma of chronic kidney disease patients but not from healthy control subjects was specifically post-translationaly modified by guanidinylation, 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 chronic kidney disease patients (88 ± 3 vs. 74 ± 10, p < 0.01). Thus, in-vitro post-translational guanidylilation of albumin might have a direct effect on the binding capacity of hydrophobic metabolites like indoxyl sulfate and tryptophan.

The used mass-spectrometry-based method was capable for the characterisation of post-translational modification of proteins, demonstrated the pathophysiological impact of a representative post-translational modification of plasma albumin and the data may help to elucidate the pathological role of protein modifications. However, the 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 at the University Hospital RWTH Aachen (Germany) is developing alternative approaches to screen plasma protein for post-translational 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/ionisation mass spectrometry for post-translational modification of the eluted proteins. Vera Jankowski told us in the interview: “The method will be adaptable to high-throughput sample handling and automated mass spectrometric analysis and therefore suited for clinical studies.”

Can we stop immunosuppression in autoimmune diseases? Newer predictive biomarkers are needed to identify patients at risk of relapse

The use of glucocorticoids with immunosuppressive drugs has been a central pillar of the therapy of immune-mediated renal disease for over 50 years. While much is known about dosing, mainly the minimization of toxicity, much less is known about the duration of therapy. This is partly due to the difficulty and cost of conducting trials over many years, and partly to the absence of reliable surrogate markers to predict which patients are at risk of relapse.

Glucocorticoid withdrawal has been shown to increase the risk of relapse in ANCA vasculitis and, in the absence of prospective trials, is suspected to be a risk factor in lupus nephritis. Yet guidelines recommend glucocorticoid withdrawal after 6 to 12 months of disease stability in vasculitis, and perhaps a longer period in lupus nephritis. Immunosuppressive withdrawal has been studied in more detail in ANCA vasculitis, where long-term therapy over four years was associated with fewer relapses and lower risk of end-stage renal failure than a shorter duration in the REMAIN trial.

There is increasing interest in biologic immunomodulators such as rituximab, yet their use has not helped with the problem of relapse, and although effective while they are being used, relapse risk rises after their withdrawal. Belimumab, an anti-BLyS agent, was not more effective than placebo in preventing relapse in a recent vasculitis trial (BREVAS), and a lupus nephritis trial is ongoing. The BREVAS trial was affected by a low relapse rate in the placebo group but, intriguingly, reported no relapses at all in belimumab-treated patients who had been induced with rituximab. Relapse after rituximab is a major problem in ANCA vasculitis and can be prevented by repeat-dose rituximab. However, combining rituximab with belimumab may be an attractive alternative and is being studied in the COMBIVAS trial.

Calcineurin inhibition is widely used in primary glomerulonephritis and has received more recent attention in lupus nephritis. The use after treatment withdrawal has been common and this has prompted use of other agents, such as rituximab. Tacrolimus induction has also been associated with a higher relapse risk in lupus nephritis, but this has not been seen with the so-called multi-target regimens, combining calcineurin inhibition with mycophenolate.

Because our therapies are largely suppressive and not curative, it is perhaps not surprising that we struggle to know when to withdraw them. Newer predictive biomarkers are required to guide physicians, and there are some examples from genomic and transcriptomic studies in development.
**Will FGF23 ever enter clinical practice? Ten years of research by nephrologists has revealed some promising clinical implications.**

Fibroblast growth factor 23 (FGF23) is the 23rd member of the FGF family of proteins, with an evolutionary story of structural modifications that, by reducing the affinity for interstitial tissues, transformed its functions from intracrine/paracrine to endocrine. Synthesized by osteocytes with a low affinity for bone matrix, FGF23 leaves bone and reaches blood to exert hormonal effects on mineral metabolism by interacting with specific receptors (FGFR) made selective by the local expression of a co-receptor, alphaklotho.

The endocrine functions first attributed to FGF23 were renal handling of phosphate and renal activation/catabolism of vitamin D. In renal tubules, FGF23 activation reducts phosphate reabsorption and inhibits lalphahydroxylation of vitamin D while at the same time increasing 24-hydroxylase. The clinical relevance of these actions was evidenced early after the discovery of FGF23 in 2000, by the identification of specific human diseases secondary to either loss-of-function or gain-of-function mutations (hyperphosphatemic familial tumoral calcinosis and autosomal-dominant hypophosphatemic rickets, respectively), or to paraneoplastic excessive extra-skeletal FGF23 synthesis (tumor-induced osteomalacia).

Based on these data, clinical interest in FGF23 could have been limited to rare diseases. However, nephrologists, attracted by the regulatory role of a new hormone involved in mineral metabolism, described for the first time in 2008 an unanticipated association of high circulating levels of FGF23 with mortality in dialysis patients. Further clinical observations evidenced a link with left-ventricular hypertrophy (LVH) in conservative renal insufficiency and, importantly, also in non-renal populations. These results prompted further translational research that demonstrated direct activation of the FGFR of cardiomyocytes by FGF23 independent of alphaklotho expression, and responsible for LVH. This result clearly offers a formidable pathomechanism linking high circulating levels of FGF23 with cardiovascular disease. In chronic renal failure patients, this association has been recently confirmed in the clinical observation of a higher risk of death in patients with progressively increasing levels of FGF23 as compared to those with stable values. Further, in non-renal populations, higher levels of FGF23 have been reported to be associated with incident coronary heart disease and with recurrent cardiovascular events and death after coronary ischemia.

But other potentially relevant pathophysiologic links are emerging for FGF23. For example, and to cite a few: FGF23 increases rapidly in patients with acute kidney injury (acute bone response to acute renal damage?); erythropoietin is capable of inducing FGF23 synthesis (renal signaling to bone?); FGF23 activates FGFR in the liver to stimulate the synthesis of inflammatory cytokines (bone link with inflammatory state?). All these data suggest potential toxicity with excess FGF23, and a therapeutic role for monoclonal anti-FGF23 antibodies. Indeed, the Food and Drug Administration (FDA) recently approved the clinical use of FGF23 antibodies in X-linked hypophosphatemic rickets. However, in uremic rats FGF23 antibodies ameliorated secondary hyperparathyroidism, but increased vascular calciifications and mortality. Thus, the complex pathophysiology of FGF23, the clinical effects of which are not limited to mineral metabolism, warrants further research with promising clinical implications.
Previous animal experimental and human studies of insulin resistance in large general populations have revealed that there is a significant link to renal disease in people with hyperinsulinemia through an effect on renal vasodilatation and subsequent increased glomerular filtration rate. The resulting glomerular hypertension and hyperfiltration can cause progressive glomerulosclerosis and renal dysfunction. Furthermore, a cluster of cardiovascular risk factors may follow leading to a progressive arteriosclerotic process with dyslipidemia, glucose intolerance and impaired fibrinolysis leading to insulin resistance syndrome and a deteriorating renal function. In several diseases such as IgA nephritis and essential hypertension a strong association, in both cross sectional and longitudinal studies, with insulin resistance has been found, especially in patients with progression of their disease. On the other side, chronic renal disorders with accumulation of uremic waste products causes insulin resistance both in muscles and in the liver and these disorders leads to increased fasting and postprandial glucose production and hyperglucagonemia as seen in type 2 diabetes. A lot of these disorders are only revealed using the systematic measurements of insulin resistance indices. There may therefore be a large group of patients with an unrecognized and unmet need for treatment. In recent years, the role of the gut hormones in the pathogenesis of impaired insulin secretion, in metabolic disorders leading to renal disease, have led to new therapeutic targets. Furthermore, the SGLT2 inhibitors may have a role in especially the liver insulin resistance seen in patients with renal disease and type 2 diabetes or prediabetes as judged from early animal and human studies. Especially the link between renal disease and hepatic insulin resistance has directed the focus on nonalcoholic fatty liver disease and the possible pathogenic role liver fat accumulation may play in diabetic patients with renal disease. A lot of studies are still needed to find the most efficient treatment of these disorders and to alleviate insulin resistance in favor of the patient.
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