



Held jointly with
Österreichische Gesellschaft
für Nephrologie



Leading European Nephrology

DAILY CONGRESS NEWS

ISSUE # 2 MAY 22nd

ISSUE 2 / MAY 22, 2016

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We are heading in the right direction, ERA-EDTA looks forward to new challenges!

Interview with the ERA-EDTA President, Professor Andrzej Więcek

Professor Więcek, you have been President for nearly two years now. Are you happy with how the ERA-EDTA has developed? What milestones have been reached?

PROF. WIĘCEK: I am very happy with the development of the ERA-EDTA, because considerable progress has been made in many fields. Take the annual congress, for example: the previous ones, and especially the last one in London, were extremely successful, and I am optimistic that this year's Congress in Vienna will be a great success as well. I am not only hinting at the proceeds we generate with congresses, although they are also important for the society, but I am very proud of the growing reputation of our Congresses. The scientific program fulfills highest standards, and we received many compliments and positive feedback over the years. At this point, I would like to thank the Scientific Committee as well as the Paper Selection Committee and all my colleagues in the Council for their hard work. We have managed to improve the quality of the Congress continuously and are now seeing the results. The number of delegates has grown, and more and more delegates from other parts of the world attend – including from Asia (mostly from Japan and South Ko-



ANDRZEJ WIĘCEK
ERA-EDTA President

rea), but also from the U.S.A., Canada and South America. This is something I am especially proud of! Another milestone is the encouraging progress made by our journals, NDT and CKJ.

Welcome Ceremony

Yesterday evening we celebrated the opening of the 53rd ERA-EDTA. Congress President Professor Gert Mayer and ERA-EDTA President Professor Andrzej Więcek greeted the nephrology community here in Vienna and announced that the congress promises to become very successful. About 8,000 delegates are expected and this high number proves the extraordinary quality of the scientific program and the growing reputation of this congress as one of the most important forums in nephrology worldwide. After the presentation of the ERA-EDTA awards – awardees were Professor Roseanna Coppo, Professor Pierre Ronco, Professor Christoph Wanner, Professor Raymond Vanholder and Doctor Emilie Cornec-Le Galland and the presentation of the ERA-EDTA Honorary Membership to Professor J. Douglas Briggs (page 3) – Professor Karl Lhotta, *(continued on page 27)*



Emilie Cornec-Le Gall received the Stanley Shaldon Award for Young Investigators

Prof. Carmine Zoccali, NDT's Editor-in-Chief, and Prof. Alberto Ortiz, Editor-in-Chief of CKJ, are doing a great job. CKJ is a very successful open-access journal now, offering very good educational materials. All the articles are also available via PubMed. NDT is currently one of the leading nephrology journals worldwide and we do believe that the impact factor of this journal will further increase in the near future. There are many other achievements which are just as important and which I would like to mention briefly. We are one of the few medical societies with our own guideline-producing body, European Renal Best Practice (ERBP). Its guidelines, position statements and comments on other guidelines enable us to provide the best standards of care for CKD patients. In addition to that we have the ERA-EDTA Registry, which, by the way, includes the extremely important the Pediatric Registry (in collaboration with ESPN), which collects and processes data on CKD in Europe and thus contributes considerably to the maintenance of high standards. We also have many successful initiatives and programs that promote basic and clinical science and others that support young nephrologists. Such programs are especially vital these days.

Why does nephrology have to focus on recruiting young colleagues?

PROF. WIĘCEK: CKD mainly affects elderly people, and due to the demographic shift the number of senior citizens is rising. As a consequence, we need more nephrologists in order to manage this workload, but the sad fact is that exactly the opposite is happening: Young doctors are more attracted

to other disciplines like cardiology, oncology, intensive medicine and other areas, while interest in nephrology is decreasing in many countries. This is an international trend, and we have to think about the reasons. Our field of specialization is rather complex, of course, and for that reason is thought to be more difficult. When you ask students, they are easily put off by topics such as acid-base disorders, electrolyte disorders, immunology, or dialysis modalities – and the complexity can indeed be discouraging. But we should emphasize that this assumed weakness of our discipline is in reality a strength: It provides a broad range of topics, offers many opportunities and helps us to acquire a very deep and detailed understanding of the complex miracle called the human body. We have to share our enthusiasm and have to ignite the spark! We can do this by stressing the importance and innovative force of nephrology. Young doctors have to understand that it is something worth getting stuck into! Can a medical society like the ERA-EDTA add to the attractiveness of a medical specialty? Yes it can, and ERA-EDTA has achieved that. It promotes scientific projects and interdisciplinary ventures and gives financial support to young colleagues. In this way, ERA-EDTA paves the way for innovations and independent science. Furthermore, it offers excellent networking opportunities. There are official collaboration agreements with other specializations, for example with cardiologists, diabetologists, organ transplant specialists, etc., and mention should also be made of our eight working groups, of course. Another thing that will add to the attractiveness of the discipline in the long term is the

European nephrology exam that we are developing. It will be an extra qualification which does not substitute national exams, but will help young nephrologists to find jobs easily in other countries and become more international. Last but not least, ERA-EDTA delivers very practical support to young doctors. There are the fellowship programs and the Young Nephrologists' Platform (YNP), of course, and it is absolutely fantastic to see how active the YNP is. They have their own CME courses and other very interesting initiatives. They have just established a mentoring program, with each mentee being assigned a mentor from another country to advise and assist him/her. I think the YNP is a very good tool for attracting young physicians – it is independent, meaning that the ERA-EDTA does not interfere directly, because young people need room for development. The young nephrologists have their own communication channels and events, but they are also fully integrated in the society's network and benefit from its experience and resources.

Is there anything special you would like to be associated with in, let's say in ten or fifteen years – for example as the "ERA-EDTA President who did this, initiated that or reorganized whatever...?"

PROF. WIĘCEK: Well, in fact I don't need to wait that long. The other Council members are already dallying with the YNP, because it was my idea many years ago and I promoted, even pushed its development. My colleagues are already joking about it, calling the YNP "Andrzej's baby". So this is something I will certainly be associated with in the future – and

ERA-EDTA MEMBERSHIP INFO

ERA-EDTA Council Members Elections

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



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

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



Leading
European
Nephrology

ERA-EDTA Membership Desk info

Are you a nephrologist? Do you want to be part of the most authoritative European Association in this field? Become a member of ERA-EDTA today! All the information at the ERA-EDTA booth in the Exhibition area or ERA-EDTA Membership Desk in the Registration Area of the Austria Center Vienna.

**Become a
ERA-EDTA Member**

www.era-edta.org



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

that's OK by me, because I'm really proud of it. The youngsters are our future, they keep our society young, alive and continually evolving!

Talking about renewal: In Europe there are probably more female than male nephrologists, but apart from Professor Jolanta Malyszko all the Council members are men. Is it time for a women's quota in the ERA-EDTA?

PROF. WIĘCEK: You are probably right there. Those nephrologists who respond to our call for candidates for the Council are mostly male, apparently. This year, there is one woman among eight candidates. You might think that's a very poor ratio – but to be honest, it was worse in previous years. Certainly we should encourage women to become active members, to run for office and to take up the positions on offer. This is something what ERA-EDTA has to face more in the future. But I must say that within the younger generation we are already seeing a larger representation of women in ERA-EDTA bodies: in fact in the YNP the current Chair is a woman and in its board there are four women, thus 40%!

What other challenges does European nephrology face? And how do you evaluate its future?

PROF. WIĘCEK: There is indeed one major challenge: We have to make nephrology fit for survival in the future. We have to be alert to keeping innovations within our field. Renal denervation, for example, was immediately taken over by cardiologists and radiologists. We have to ensure that we nephrologists do not surrender innovations willingly to others and end up with a reputation of being poor innovators ourselves. On top of that, we have to step up our activities in the policymaking sphere – many hospitals in Europe have cut the number of nephrological beds, even the number of nephrological wards has been reduced. Dialysis is often done by intensive care doctors in these clinics – but we have to get out the message that nephrology is much more than just performing dialysis therapy. We need to sharpen our profile and our image: We should be perceived not only as the doctors who provide dialysis treatment, but as doctors who can prevent the necessity of renal replacement therapy (RRT). As such, we would be invaluable to the medical world. The population is growing older, many more people need expensive RRT – and we are the specialists who can effectively slow the progress of CKD and thus save the medical system millions of Euros. Opinion leaders and policymakers need to know this – and we are working hard to get that message through. In this regard, our partnership with the European Kidney Health Alliance (EKHA) is extremely helpful, with direct contacts to the European Parliament. I am very happy that ERA-EDTA's past president, Professor Raymond Vanholder, is now the Chair of EKHA. He knows our aims and is passionately pursuing them. Of course, we still have a long way to go, but we are heading in the right direction. I am optimistic that nephrology has a bright future! ■

Expert in Interview

► **PROF. ANDRZEJ WIĘCEK**
President ERA-EDTA



ERA-EDTA Awards 2016

Professor Roseanna Coppo received ERA-EDTA Award for Outstanding Contributions to Nephrology



Professor Rosanna Coppo, Italy, is one of four recipients of the 2016 ERA-EDTA Award for Outstanding Contributions to Nephrology. She dedicated her career to improve education in nephrology. From 2003 – 2009 she was responsible for the Continuing Medical Education (CME) programme of the ERA-EDTA. In 2013, she chaired the Scientific Committee of the ERA-EDTA Congress in Istanbul as well as scientific committees of other associations. Professor Coppo contributed to education also by working in editorial boards of many journals: NDT, CJASN, Paediatric Nephrology, Journal of Nephrology and Giornale Italiano di Nefrologia. During her successful career Professor Coppo trained numerous nephrologists and pediatricians but also she contributed to establish the education of nephrology on institutional level what makes this award very well deserve

Professor Pierre Ronco received ERA-EDTA Award for Outstanding Basic Science Contributions to Nephrology



Professor Pierre Ronco, France, is the recipient of the 2016 ERA-EDTA Award for outstanding basic science contributions to nephrology. His main fields of interest in clinical and scientific research are the pathophysiology and treatment of immunological diseases of the kidney. Professor Ronco contributed to the characterization of megalin, the target antigen of pathogenic antibodies in Heymann's nephritis, a rat experimental model of membranous nephropathy (MN). Besides, he also contributed to the identification of neutral endopeptidase (NEP) and dipeptidylpeptidase IV (DPPIV) as new antigens involved in MN. Last but not least, he established his reputation as a pioneer in nephrology by identifying a novel autosomal dominant hereditary collagen disease, which he called HANAC for Hereditary Angiopathy with Nephropathy, Aneurysms and Cramps.

Professor Raymond Vanholder received ERA-EDTA Award for Outstanding Contributions to ERA-EDTA



Professor Raymond Vanholder, Belgium, is the recipient of the 2016 ERA-EDTA Award for outstanding contributions to ERA-EDTA. The past-president of the ERA-EDTA gave the society a wider scope and initiated many new projects during his presidency: The 3rd Research Program call was opened, over 100 CMEs were organized, 3 new Working Groups were installed (DESCARTES, Diabesity and CKD-MBD) and the Young Nephrologists' Platform was launched. He introduced a more functional website with a fresh look and took care that ERA-EDTA is present on social networks. All the above is only a tiny part of Professor Raymond Vanholder's activities and contributions to the ERA-EDTA but it shows that he fully deserves the Award Outstanding Contributions.

Professor Christoph Wanner received ERA-EDTA Award for Outstanding Clinical Science Contributions to Nephrology



Professor Christoph Wanner, Germany, is the recipient of the 2016 ERA-EDTA Award for outstanding clinical science contributions to nephrology. The main achievements in research field are the design and execution of two landmark trials (4D & EMPA-REG Outcome Studies) impacting on cardiovascular and renal health in type 2 diabetes. Through their results these studies stimulated the field in multiple directions and revolutionized therapy of type 2 diabetics in early and late stages of CKD and on dialysis. The studies on the activated acute phase response predicting outcomes in dialysis patients were forerunners in the field. Besides, Prof. Wanner contributed a lot to the ERA-EDTA: In 2003 he was elected Registry Board Member, transitioning to Chair of the ERA-EDTA Registry in 2009 where he served until 2015.

And the Stanley Shaldon Award for Young Investigators went to... Dr. Emilie Cornec-Le Gall



The Stanley Shaldon Award for Young Investigators honors outstanding young researchers and clinicians. For this award, the Award Committee chooses among the best young authors of abstracts presented during the past three years at the ERA-EDTA Congresses. The winner receives 10,000 EUR and will also become an ex-officio member of the Young Nephrologists' Platform Board. In 2016, the Stanley Shaldon Award for Young Investigators goes to Dr. Emilie Cornec-Le Gall, France, who is currently working as Post-doctoral Research Fellow in PC Harris lab (ASN fellowship), Division of Nephrology and Hypertension, Mayo Clinic, Rochester MN, USA.

The ERA-EDTA: an actively networking society

The information age in which we live means that networking is becoming more and more vital. The ERA-EDTA does not close its eyes to that trend, but at different levels has established an extensive network of its own in recent years.

At the international level, it collaborates closely with the two other major international organizations, namely the American Society of Nephrology (ASN) and the International Society of Nephrology (ISN). There is an intensive exchange of ideas and information within these partnerships, including joint sessions at the respective congresses. One example is the 'ASN Highlights symposium' at our own congress this year (see below). "We follow the same goal of advancing education, research and science to achieve the highest quality care for everyone with kidney disease. So working closely together is an obvious option", explains Professor Dr. Andrzej Więcek, President of the ERA-EDTA.

Another important nephrological partner at national and international level that is similarly represented at our congress with its own symposium is DOPPS (see p. 6). Two years ago, ERA-EDTA and Arbor Research signed a collaboration agreement for the creation of EURODOPPS. The formal partnership with ERA-EDTA and regular transfer of EURODOPPS data to the Registry has enhanced the use of these data to address scientific and policy issues of interest to ERA-EDTA, the European nephrological community as well as health care authorities.

ERA-EDTA also works together with the various national societies of nephrologists. Each year, it invites the Member State national societies to networking events at which joint projects are discussed and important research alliances are forged (see p. 27). ERA-EDTA thinks beyond boundaries in this respect as well – it is particular proud of its excellent cooperation with the two major organizations in Asia, the Chinese Society of Nephrology and the Society of Nephrology. A joint symposium is being held with each of these partners in Vienna (see below).

Furthermore, ERA-EDTA is also involved in active, interdisciplinary exchange and is engaged in partnerships with the societies of other disciplines, including the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). At the congress in Vienna, ERA-EDTA is organizing a symposium with each of these two partners.

ERA-EDTA also collaborates closely with EuroPD, an organization dedicated to the advancement of PD therapy in Europe, which is driven by basic and clinically applied scientific advance. Yesterday, on 'Working Groups' day, EuroPD held a successful symposium at the ERA-EDTA Congress. Intensive interdisciplinary networking is also conducted at the ERA-EDTA Working Groups level. The DESCARTES CME that took place yesterday was organized in collaboration with EKITA, a branch of the European Society of Organ Transplantation. Further CME courses also took place in collaboration with the EAU Section of Urolithiasis (EULIS) and with the European Association of Rehabilitation in Chronic Kidney Disease (EURORECKD). In addition, a mini-lecture has been organized in collaboration with the International Association for the History of Nephrology (IAHN).

Last, but not least, ERA-EDTA also maintains close relations with that highly renowned journal, 'The Lancet'. This afternoon there will be a joint symposium at which landmark nephrology papers published in the 'The Lancet' will be presented and discussed (see below).

All in all, the ERA-EDTA is actively networking to gain best results and exploit synergies in order to promote nephrology worldwide. ■



Leading European Nephrology

15.15 – 16.45, HALL A

ASN Highlights

- Glomerular Diseases – Brad Rovin, Columbus, U.S.A
- Transplantation – John Friedewald, Chicago, U.S.A
- ESRD – Speaker to be confirmed

17.00 – 18.30, HALL A

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

- The DOPPS Program continues to grow and invites collaborators – Francesca Tentori, Ann Arbor, U.S.A.
- Key lessons from the first 20 years of DOPPS – Michel Jadoul, Brussels, Belgium
- Guideline adherence and drug prescription in EURODOPPS – Findings from the first proposal call – Sophie Liabeuf, Amiens, France
- CKDopps: Improving outcomes in advanced CKD and the transition to dialysis – Ziad Massy, Paris, France
- PDOPPS: the largest international study of PD practices – Simon Davies, Stoke-On-Trent, United Kingdom

17.00 – 18.30, HALL A

ERA-EDTA & ESC (European Society of Cardiology) – Joint Symposium

- Cardiac function in CKD patients: how valuable are ECHO and biomarkers? – Carmine Zoccali, Reggio Calabria, Italy
- Pathophysiology of hypertension in chronic kidney disease – Michel Burnier, Lausanne, Switzerland
- Uncontrolled hypertension – how to prevent unfavourable kidney outcome? – Andrzej Wiecek, Katowice, Poland
- How low should blood pressure be lowered to protect the kidney in chronic kidney disease – Josep Redon, Valencia, Spain

10.45 – 12.15, HALL A

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

- The kidney as a target of high blood pressure – the evidence in 2016 – Johannes F.E. Mann, Munich, Germany
- Renal angioplasty – is there still an indication in hypertensive CKD patients with RAS? – Patrick Rossignol, Vandoeuvre-Les-Nancy, France
- Which future for the treatment of hypertension with renal denervation? – Roland E. Schmieder, Erlangen, Germany
- Management of hypertension in patients with CKD – Michel Burnier, Lausanne, Switzerland

15.15 – 16.45, HALL D

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

- The mechanisms of AKI to CKD continuum – Motoko Yanagita, Kyoto, Japan
- Outcome of CKD-MBD: pathophysiology and management – Masafumi Fukagawa, Isehara, Japan
- Biomarkers of progressive renal disease – are we looking for the right ones? – Gert Mayer, Innsbruck, Austria
- Lipoproteins and outcome in CKD – the other view – Danilo Fliser, Homburg / Saar, Germany

11.45-13.15, HALL E

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

- Renal Replacement Therapy in Europe and in China
- Transplantation data from Europe – Rainer Oberbauer, Vienna, Austria
 - European perspective of dialysis based on the ERA-EDTA Registry data – Kitty Jager, Amsterdam, The Netherlands
 - CKD in China: current and perspective – Xueqing Yu, Guagnzhou, China
 - Extracorporeal therapies in critical care nephrology: experience from China – Yongchun Ge, Nanjing, China

15.15 – 16.45, HALL D

The Lancet / The Lancet Diabetes and Endocrinology

I think we should also support measures that are not kidney-specific but lifestyle-oriented

Interview with Professor Raymond Vanholder, Chairman of the European Kidney Health Alliance (EKHA)



RAYMOND VANHOLDER
Ghent, Belgium
Chairman of the European Kidney Health Alliance (EKHA)

Prof. Vanholder, you are the Chairman of the European Kidney Health Alliance (EKHA). Could you briefly describe its mission, aims and objectives?

VANHOLDER: EKHA is an alliance of non-profit organizations representing key European stakeholders in kidney health issues. The aim is to reduce the incidence and impact of kidney disease in Europe. This can be achieved by either stimulating research or by raising awareness at the political and socioeconomic level. Which brings me to the key mission of EKHA: We try to convince European politicians that CKD prevention and early detection is vital and that treatment, education and research should be further improved. We are engaged at the European level, but work closely together with the national societies of nephrology and encourage them to influence policymaking in their respective countries as well.

A year ago you took over the presidency of EKHA. What, in your eyes, are the most urgent tasks EKHA has to deal with?

VANHOLDER: Right now we are focusing on prevention. This is an important goal, but not at all easy to reach. As you know, European countries are very heterogenic – so it is difficult to implement a common strategy. Yet this is exactly what we need to work towards. We need to communicate to every European country that CKD prevention measures will pay off. What has to be spent should be seen as an investment in the

health and future of a country, and not as costs. Of course, more research on socio- and health-economic aspects is required in order to prove that the national economy benefits from CKD prevention, so this is something EKHA wants to initiate as well.

What, in your experience, is the best argument for persuading policymakers to take an interest in kidney health and to take action against the rising prevalence of end-stage renal disease?

VANHOLDER: Well, that's an easy question to answer – It's always a matter of money, so we therefore need to provide more health-economic data.

Which milestones have already been reached by EKHA – and which new milestones have been set?

VANHOLDER: Last year we published the 'Recommendations for Sustainable Kidney Care', with which we gained worldwide recognition. The recommendations were based on two papers on the costs of kidney disease – one was published in 'The Lancet', the other in NDT. So that was important, but I think it's now time for a broader perspective. We should focus not only on CKD, but also on primary prevention in general. In most cases, kidney disease develops at the end of a chain of other events or factors. An unhealthy lifestyle leads to diabetes and hypertension, and these diseases can cause CKD. So I think we should also support measures that are not kidney-specific but lifestyle-oriented, for example the Dutch initiative to improve food quality by reducing fat and salt and sugar in processed food. Belgium and the UK have already managed to decrease the daily salt intake of the population by 1g, simply by reducing the salt content in bread – and I think these kinds of programs will help in the long run to maintain public health. They may have greater and positive impacts on health and also on kidney health than expensive screening programs. And if a certain measure proves to be successful in one EU country, it would be a good strategy to implement it in other countries as well. So this is something we have to work towards in the future and this is why networking is that important! ■



Video Message

► **KARIN KADENBACH**

Member of the European Parliament;
Chair of the MEP Group for Kidney Health

Karin Kadenbach is an Austrian social democrat politician. She has been a member of the European Parliament since 2009. Within the Parliament, she is a member of the Committee on Environment, Public Health and Food Safety (ENVI Committee), the Committee on Agriculture and Rural Development, as well as the Committee on Budgetary Control. In addition, Karin Kadenbach is Chair of the MEP Group for Kidney Health, which collaborating closely with the European Kidney Health Alliance (EKHA) and ERA-EDTA.

In her role as Chair of the MEP Group for Kidney Health, she sent a welcoming address to the ERA-EDTA Congress. The video message was shown during yesterday's Opening Ceremony. You can watch it here:



Today's Highlights

Plenary Lecture 1

10.45 - 11.30, HALL A

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

Late Breaking Clinical Trials

11.45 - 13.15, HALL A

The therapeutic evaluation of steroids in iga nephropathy global (testing) study – Hong Zhang

Early versus late initiation of renal replacement therapy in critically ill patients with aki (the elain-trail) – Alexander Zarbock

Elbasvir / grazoprevir treatment of hcv infection in patients with ckd stage 4 / 5: clinical, virologic, and health-related quality of life outcomes in the c-surfer study – Annette Bruchfeld

Lipoprotein(a) – a double-edged sword in cardiovascular disease – Winfried März

Marsupialized catheter and incremental dialysis dose, the key to increase peritoneal dialysis prevalence in elderly – Hilary Riva

Sodium excretion and the risk of cardiovascular disease in persons with chronic kidney disease – Jiang He

This study will be presented on Tuesday, 14.45, Session "Salt on the Table"

The Lancet / The Lancet Diabetes and Endocrinology Symposium

15.15 - 16.45, HALL D

20 Years of the DOPPS Program

The Dialysis Outcomes and Practice Patterns Study (DOPPS) Program is celebrating its 20th anniversary in 2016. The DOPPS Clinical Symposium at the ERA-EDTA Congress will highlight the accomplishments of the program and look forward to future research.

Background

Throughout the history of the DOPPS Program, a key motivation has been to understand the reasons for international variation in dialysis and chronic kidney disease (CKD) outcomes. As such, the goals of the DOPPS Program have been:

1. Describing variation in treatment practice across participating countries.
2. Analyzing variations in clinical practice patterns and associating them with clinical outcomes such as mortality, hospitalization and quality of life with the goal to help identify optimal practices.
3. Translating findings to improve care.

In addition to publishing in peer-reviewed journals, the goal is to communicate key messages that can be readily implemented.

Lessons from the DOPPS

Research from the DOPPS over the past 20 years has examined the need to for surgical vascular access for most dialysis patients. Vascular access use varies greatly within and across countries even now. In countries such as the UK and US, a culture devoted to raising surgical vascular access use has led to commendable improvements. By contrast, fistula use has fallen and / or catheter use has risen in other countries. The DOPPS has also looked at dialysis session length, demonstrating that patients who receive longer sessions have lower mortality rates. This finding was in part the basis for policy changes in Germany and Japan; each country now has among the longest average dialysis session length in the international DOPPS. The DOPPS has been at the forefront of studying the experiences of dialysis patients, collecting information directly from study participants. DOPPS publications showed, for example, that lower quality of life and symptoms of depression predicted higher mortality rates amongst hemodialysis patients. As the renal community becomes more aware of the importance of quality of life as a key outcome, DOPPS data can be leveraged to identify fac-

tors of greatest importance to patients and develop novel instruments to assess them.

EURODOPPS

EURODOPPS is a joint venture of the DOPPS and the ERA-EDTA to collect and analyze data to address questions that are of specific interest to the European community. Since its start in 2014, EURODOPPS has grown in a fruitful collaboration among investigators on both sides of the ocean. The enthusiasm and number of European researchers applying to use EURODOPPS data to address specific research projects demonstrates the interest of the community in this endeavor. To date, six investigators were awarded this opportunity, including one project that will be announced at the 2016 ERA-EDTA congress in Vienna.

The Peritoneal Dialysis Outcomes and Practice Patterns Study

The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) was launched in 2012. It is coordinated by Arbor Research in collaboration with the International Society for Peritoneal Dialysis (ISPD). Data is collected in Australia, Canada, Japan, the United Kingdom, and the United States. Even at this early stage, the PDOPPS sample already represents the largest international study of PD patients. With data collected, the study serves as an invaluable resource and research platform for the international PD community, and provides a means to understand variation in PD practices and outcomes, to identify optimal practices, and to ultimately improve outcomes for PD patients.

Chronic Kidney Disease Outcomes and Practice Patterns Study

The Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) is now launched in Brazil, France, Germany, Japan and the U.S. In France, CKDopps is part of the CKD-REIN cohort. The CKDopps was developed to address the difficulty of studying patients as they transition from advanced CKD to kidney failure. The motivation for the study is that

much of the variation in patient outcomes for advanced CKD patients is likely attributable to practice differences in 'real-world' settings.

Collaborations

The DOPPS is committed to collaboration with external investigators to maximize the scientific value of the wealth of data made possible by all the participating facilities and patients. To continue the tradition of providing unique opportunities for scientific investigation, the DOPPS invites interested researchers to learn more about possible collaboration with us. For more information, please visit www.DOPPS.org ■



The DOPPS Program: Celebrating 20 Years and Looking Ahead

Monday, 23-05-2016, 17.00 – 18.30, HALL A

Chairpersons: Bruce Robinson, Friedrich Port

- **The DOPPS Program continues to grow and invites collaborators** Francesca Tentori
- **Key lessons from the first 20 years of DOPPS** Michel Jadoul
- **Selected findings from the first EURODOPPS call for proposals** Sophie Liabeuf
- **CKDopps: Improving outcomes in advanced CKD and the transition to dialysis** Ziad Massy
- **PDOPPS: the largest international study of PD practices** Simon Davies



ROBERTO PECOITS-FILHO
Curitiba, Brazil

Optimal timing of dialysis initiation and modality selection: preliminary findings of the CKDopps

The burden of chronic kidney disease (CKD) is rising internationally, consequent to an aging population and rises in prevalence of CKD-associated conditions, including diabetes, hypertension, and obesity. The transition from CKD in its later stages to renal replacement therapies (RRT) is a time of particularly high clinical risk with profound effects on mortality, morbidity, quality of life (QOL), and health resource utilization. In fact, based on the current practice patterns, mortality is consistently highest in the first 3 months after initiation of dialysis. These strikingly elevated mortality rates highlight the importance of studying the care of patients in this transition to improve patient outcomes.

Associative data based on registries and prospective cohorts suggest that early and consistent predialysis care leads to better outcomes, including greater use of home-based ther-

apy, diminished use of hemodialysis catheters, and improved early and late survival. Also, the optimal timing of dialysis initiation has remained uncertain, and estimated glomerular filtration rate (eGFR) at dialysis start varies widely within and between centers. Recently, the IDEAL clinical trial brought new information to this important issue, showing no difference in mortality between the early and late dialysis initiation groups. Seventy-six per cent of the patients in the late group started dialysis with creatinine clearances higher than the intended 7 mL / min / 1.73 m², the majority due to uraemic symptoms. The average clearance at the time of starting dialysis was 12.0 and 9.8 mL / min / 1.73 m² in the early and late groups, respectively. Yet the late group started dialysis on average 6 months later than the early group. While former guidelines may have contributed to earlier dialysis initiation, current recommendations tend to favor later dialysis start, as they suggest beginning dialysis at eGFR well below 10 ml / min / 1.73 m² with close monitoring of uremic symptoms that may trigger an earlier start in particular subgroup of patients.

Despite the presence of these guidelines, there is an impressive international variation in dialysis initiation practices. United States Renal Data System (USRDS) data have shown trends of increasing eGFR at dialysis initiation in the United States since 1995 (but stable since 2010), and the Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrates that eGFR at dialysis start is higher in Belgium, the United States, Germany, and Canada than other countries.

While analyses of DOPPS, USRDS, and other data are limited to patients who start dialysis, the CKDopps aims to study the transition to end-stage kidney disease (ESKD) more thoroughly by following patients prior to initiation of dialysis, including those who may die prior to reaching ESKD, which is common among those with comorbidities. By allowing for comprehensive, prospective analyses of practices and outcomes prior to and during the transition to dialysis, CKDopps findings are expected to inform practices and guidelines to improve this transition, including vascular access placement, medication usage, optimal eGFR at initiation of dialysis, and

Sunday, 22nd MAY, 2016
h 13:30/15:00 - Hall K, Level -2

CHIESI PRODUCT SYMPOSIUM

Advancements in immunosuppression: are all tacrolimus formulations the same?

Chaired by Prof. R. Oberbauer (Austria)

Control and optimization: the answer in PK

Prof. P. Marquet (France)

Management and clinical outcomes: the answer of the clinician

Prof. J. Pascual (Spain)

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CKD education, and to help identify patient subgroups in which deviations from overall practice recommendations may be appropriate. Improvements in some or all practices may provide means to reduce unplanned dialysis starts, which remain far too common internationally.

In the CKDopps population, there is substantial variation in anemia prevalence and management between countries. For patients with hemoglobin (Hgb) <11 g/dL, <50% were prescribed either iron or an erythropoiesis-stimulating agent (ESA) in France and the United States, and a high percentage of patients did not have iron indices measured. ESA and iron use in patients with Hgb <11 g/dL was more common in Brazil and Germany than in France and the United States; these treatment differences did not fully explain the observed differences in Hgb levels between countries. Future analyses will investigate associations of anemia prevalence and management with patient and treatment characteristics, as well as with clinical and patient-reported outcomes.

Finally, Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that CKD patients receive information

on CKD and all RRT modalities. Even when education is provided, patients' understanding of such a complex topic may be limited. A recent analysis of perspective on education received regarding kidney disease and RRT options, based on early data from over 3,000 CKDopps participants to date, in 5 different countries shows that patients with more advanced CKD were more likely to have received some education, on kidney disease and / or on RRT options. However, in stage 4 CKD, 77% or more of patients in Brazil and France, and 62% in the United States reported not having received any education. In stage 5 CKD, this percentage decreased to ~40% in the United States, but remained high in Brazil (72%). In each country, >60% of stage 4 patients did not know what RRT option they would choose if their kidneys completely failed. Even in stage 5 CKD, more than a third of patients didn't express a preference (United States: 32%; Brazil: 38%); in fact, a sizable number of patients (United States: 16%; Brazil: 38%) reported they had never discussed RRT options with their doctor. In fact, retrospective analysis of the global DOPPS shows a huge variation in the number of days before dialysis initiation that patients were in contact with a nephrology team. Despite receiving nephrology care, the great major-

ity of CKD stage 4 patients reported they had not received any formal education. Even among patient with more severe CKD (stage 5), a high percentage reported no education, and displayed substantial uncertainty regarding the choice of RRT.

In summary, the transition from advanced CKD to RRT is a complex phase in the treatment of CKD patients, and still not very well studied. There is no doubt that careful and integrated pre-dialysis care influences clinical outcomes, dialysis take-on rates, and modality selection. However, the optimal timing for dialysis initiation and the ideal modality choice for individual patients remain to be defined, but ongoing studies, such as the CKDopps may shed important light in these important issues. ■

Symposium 8
Should PD as initial dialysis modality
become the standard of care?
Sunday, 11.45 - 13.15, HALL E



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CARSTEN BERGMANN
Ingelheim am Rhein, Germany

Optimizing the management of ciliopathies and cystic disorders

Genetic testing holds the key to accurate diagnosis and effective treatment

Separate polycystic kidney disease (ADPKD / ARPKD) from others

Cystic nephropathies encompass a clinically and genetically heterogeneous group of diseases. With a prevalence of around 1 in 500, they include the autosomal dominant (ADPKD) and autosomal recessive (ARPKD) forms of polycystic kidney disease (PKD), cystic dysplastic disorders, as well as the nephronophthisis (NPHP) complex and other medullary cystic kidney diseases. The products of the responsible genes are referred to collectively as 'cystoproteins' and primarily localize to the cilia / centrosome complex. Cilia are antenna-like projections on the surface of most cells that enable an intensive information exchange within and between cells, and are essential for regulating the cell cycle. Structural and functional defects in these structures lead to a wide variety of conditions known collectively as ciliopathies.

NGS multi-gene nephro panels: Compass in the jungle

Differentiation of the various entities can be very difficult. Important contributions to a classification are provided by genetics, which has improved considerably in recent years with the advent of high-throughput, next-generation sequencing (NGS). The increasing number of genes largely benefits from NGS-based approaches that allow the parallel analysis of all disease genes, for example, by the use of multigene panels.

Affected gene and type of mutation correlate with clinical course

ADPKD is the commonest life-threatening genetic disease and affects 10-15 million people worldwide. The majority of patients exhibit a mutation in the PKD1 gene, and around 15-20% exhibit a mutation in the PKD2 gene. Although ADPKD primarily affects the kidneys, it is a multisystem disease with a progressive course and with profound extrarenal involvement. The prominent clinical signs are hypertension and a progressive deterioration in renal function, accompanied by a volume increase in both kidneys caused by massive cyst formation. Patients with a PKD2 mutation exhibit, on average, a significantly milder course of the disease than PKD1 patients and a lower prevalence of urinary tract infections and arterial hypertension. PKD1 patients reach ESRD on average 20 years earlier than PKD2 patients (at 58.1 vs. 79.9 years of age). Not only the affected gene but also the type of PKD1 mutation correlates significantly with the absolute renal survival time.

Genetics explains early and severe cases of ADPKD

The clinical symptoms generally do not emerge until adulthood, but can be considerably variable even within the same family. About 2-5% of patients already show clinical signs perinatally or in childhood. Family studies show that there is a high recurrence risk of 50% in siblings of early-manifesting patients. A genetic principle that helps explain the high recurrence risk in families with the early manifesting form has recently been described. Accordingly, a portion of the early and severely affected patients carry a mutation in more than one gene, or more than one gene copy is affected in the case of dominantly transmitted genes (in the sense of a so-called increased mutation load).

Mutation analysis not necessary in everybody, but useful in certain patients

While ultrasound evidence of three or more renal cysts (uni- or bilateral) in persons under the age of 40 who, on account

of their family history, are at increased risk of developing ADPKD is regarded as supporting the diagnosis, a mutation analysis might prove useful in the discussion of different clinical settings:

- For diagnostic confirmation in patients with a cystic nephropathy of uncertain origin (for example, in the absence of a positive family history).
- Assessment of comorbidities and possible complications.
- Discussion of (novel) therapeutic options.
- To determine the recurrence risk for the patient's own children (50% in case of dominant inheritance vs. <1% in case of recessive disease).
- When assessing the recurrence risk for other family members.
- In the context of a living kidney donation to exclude carriage in the case of younger donors.
- In early and severely affected families, discussion of prenatal diagnosis such as preimplantation genetic diagnosis (PGD).

Hereditary tumor syndromes with cystic kidneys

ADPKD is sometimes referred to as 'neoplasia in disguise'. Fortunately, however, carcinomas rarely develop in ADPKD despite the frequency of hyperplastic polyps and microscopic adenomas. The term 'neoplasia in disguise' also alludes to certain similarities and correspondences between ADPKD and hereditary tumor syndromes with cystic kidney changes such as von Hippel-Lindau (VHL) disease and tuberous sclerosis complex (TSC). TSC and VHL can also be described as ciliopathies and exhibit, just as in ADPKD and many tumors, an upregulation of the mTOR signaling pathway.

The recessive form of PKD (ARPKD) can affect adults and can mimic ADPKD

The synergistic role of polycystin-1 and the TSC2 gene product tuberin is also suggested by the severe and early-onset phenotype in patients harboring a deletion encompassing the adjacent TSC2 and PKD1 genes. These patients may sometimes mimic ARPKD, which is typically a pediatric disorder. It is however important for an adult nephrologist to know that the clinical spectrum in ARPKD is far broader and only moderately affected adult patients with ARPKD have been described. With advancing clinical course, the kidney structure may increasingly resemble that of ADPKD due to the formation of larger cysts and increasing interstitial fibrosis. Hepatobiliary complications resulting from the inevitable presence of congenital hepatic fibrosis can dominate the clinical picture, in particular in the case of older patients, and progressive portal hypertension can lead to consequential complications such as hypersplenism and esophageal varices. Most patients exhibit a mutation in the PKHD1 gene, however greater heterogeneity has been revealed in recent years.

HNF1B: Frequent cause for cystic dysplastic kidneys, but may look like PKD

The course of cystic dysplastic kidneys (congenital anomalies of the kidney and urinary tract, CAKUT) is very varied. The kidneys often lose their reniform character, and the ultrasonographic pattern is irregular with excessive connective tissue in between various sizes and locations of cysts. Dysplasia and renal agenesis are also typical manifestations of the autosomal dominant inherited renal cyst and diabetes syndrome (RCAD), which is caused by mutations of the TCF2 / HNF1B gene. The manifestation spectrum is broad and can encompass a range of changes besides cystic kidneys (diabetes / maturity onset diabetes of the young (MODY), genital abnormalities, hyperuricemia, hypomagnesemia, elevated liver enzymes). However, the disorder

frequently manifests monosymptomatically. A substantial proportion of the mutations (approximately 30-50%) are large deletions

Practically no recurrence risk for families with *de novo* mutations

The genetic classification is also particularly important for patients and families because about half of all HNF1B mutations occur *de novo* (in ADPKD 10-20%) and in these cases there is practically no increased recurrence risk, which can be a great relief to the families involved.

Nephronophthisis (NPHP) and related ciliopathies

Cystic kidney changes can also arise in nephronophthisis (NPHP) and medullary cystic kidney disease (MCKD) as well as the syndromic ciliopathies that show considerable overlap. Nephronophthisis (NPHP) represents the most frequent genetic cause of kidney failure in children and young adults, and typically presents initially with a urinary concentrating defect. Whilst being especially heterogeneous clinically and genetically, all NPHPs have in common an autosomal recessive inheritance pattern and a tubulointerstitial / cystic character. To date, more than 20 NPHP genes have been described and further heterogeneity can be expected. NPHP1 is the most frequently affected gene with 20-40% of patients carrying a homozygous NPHP1 deletion; the other genes make only a small contribution, so a NGS diagnostic panel is advantageous in this case. Furthermore, most NPHP genes behave pleiotropically; i.e. they can cause a much broader phenotypic spectrum than just isolated nephronophthisis (for example, Senior-Loken or Joubert syndrome).

MCKD / ADTKD: Dominant nephronophthisis?

Medullary cystic kidney disease (MCKD), which is also tubulointerstitial in character, is often but simplistically regarded as the autosomal dominant counterpart of NPHP (NPHP-MCKD complex) with a generally less severe course than the recessive forms and a usually later onset in adulthood. Renal failure usually occurs between the third and sixth decade of life, with tubular atrophy and interstitial fibrosis evident in the biopsy. A new nomenclature for this group of diseases is currently being discussed (autosomal dominant tubulointerstitial kidney diseases, ADTKD).

For a long time, the only known related gene was UMOD (MCKD2). This gene encodes uromodulin, also known as Tamm-Horsfall protein, which is the most abundant protein in the urine of healthy individuals. UMOD mutations can lead to various types of tubulointerstitial nephropathy, including glomerulocystic kidney disease and familial juvenile hyperuricemic nephropathy. Only recently has MUC1 been identified as the gene underlying MCKD1. A **hotspot mutation in MUC1 explains a considerable proportion of patients**. This can be verified by a simple and cost-effective test with a high detection rate. Further genes known to be involved in ADTKD are REN and HNF1B.

Genetic diagnosis directs clinical decision-making

Genetics is increasingly being used to direct clinical decision-making and a close interdisciplinary cooperation and dialogue between nephrologist and geneticist is beneficial. NGS will continue to simplify diagnostic testing while technical capabilities have been enhanced. Many clinical laboratories are now offering an ever-increasing catalogue of genetic tests including single genes, multigene panels, exomes, genomes, transcriptomes, and epigenetic assays. Opportunities and shortcomings of various approaches in different clinical settings need to be balanced. Substantial challenges and increasing complexity arise from data storage and bioinformatic and interpretative issues. Interpretation of the obtained data and not the primary wet lab procedure is the most challenging part of the analysis and *(continued on page 10)*

Rare Disease Expert Forum

Advancing the Management
of Rare Diseases

Rare Renal Diseases Are Growing Up Lunch Symposium at the 53rd ERA-EDTA Congress

Chaired by Prof. Rainer Oberbauer, Vienna

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

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

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

Hall N - Level 1

13:45 Chairman's welcome

Prof. Rainer Oberbauer, Vienna

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

Dieter Haffner, Hannover

14:05 Managing the Adolescent Patient

Larissa Kerecuk, Birmingham

14:20 Cystinosis in Adults ; An Emerging Population

Albane Brodin-Sartorius, Paris

14:30 Discussion

14:40 Closing remarks

Lunch boxes will be provided

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(continued from page 8) requires expert knowledge in genetics and of the respective specialized medical field. In future years, whole-genome sequencing (WGS) may eventually serve as a universal first-line test for any disorder with a suspected genetic origin. However, for the time being, a one-size-fits-all approach is not reasonable and many arguments in favor of a more differentiated approach dependent on the patient's phenotype are present.

Conclusions for clinical practice

- It is only possible to provide accurate genetic counseling and discuss the expected clinical course, spectrum of symptoms (with early detection and treatment

of complications), and recurrence risk if the underlying genotype is known.

- The new methodology of next-generation sequencing (NGS) often provides significant advantages in terms of diagnostic cost, efficiency and informativeness.
- NGS is increasingly replacing the classical stepwise analysis ('gene-by-gene' analysis) for heterogeneous diseases.
- Especially for young patients, genetic diagnosis often provides a clear-cut assessment of the disorder and improved clinical care (with, amongst other things, early detection and monitoring of the renal or extrarenal manifestations to be controlled).

- The underlying mutation may have consequences for the therapeutic approach and is also important with regard to prognosis and recurrence risk in the context of transplants. ■

Symposium 10
Actualities in hereditary disorders
Sunday, 11.45 – 13.15, HALL B



FRANK A. FLACHSKAMPF
Uppsala, Sweden

Non-invasive assessment of cardiac structure and function: what nephrologists must know

The role of echocardiography, troponin and natriuretic peptides

otensin-enzyme converting (ACE) inhibitor therapy than with other drugs. Progressive increase in mass under dialysis is a further negative prognostic factor.

Impairment of LV systolic and diastolic function. Coronary artery disease may lead to myocardial infarct with attending decrease in LV ejection fraction (LVEF), but diffuse reduction in contraction also occurs—for example, as diabetic cardiomyopathy—and is better identifiable by longitudinal strain measurements than by ejection fraction. Impaired diastolic function is present in most patients. The clinical syndrome of heart failure is difficult to define in patients undergoing dialysis due to the periodic changes in volume status. This problem is compounded by the lack of specificity of elevated natriuretic peptides. EF, the classic echocardiographic LV function parameter, is difficult to measure and has low reproducibility. Furthermore, it does not identify diastolic dysfunction. Therefore, classic volume-based parameters need to be supplemented with information about longitudinal LV function, most importantly early mitral annular velocity (e') and global longitudinal strain, which are sensitive to both systolic and diastolic functional abnormalities.

LV and left atrial volumes are often increased. The reasons are multifactorial, including systolic and diastolic LV function, increased cardiac output due to shunts, atrial fibrillation, mitral or aortic regurgitation, and others.

Right-ventricular (RV) function systolic is often decreased, with or without concomitant pulmonary hypertension, and is an only recently recognized important independent prognostic parameter.

Calcification of the aortic and mitral valve, typically with changes located primarily at the base of the cusps, leads to or accelerates valvular heart disease, mostly aortic stenosis and mitral regurgitation.

Serum biomarkers such as troponins and C-reactive protein have clear prognostic power in patients with renal failure, but are relatively unspecific and often unhelpful in the individual patient. The same applies to (NP), which are invariably elevated; NT-proBrainNP is believed to be more strongly correlated with GFR and thus less informative about cardiac function than BrainNP. NP can still be used as tests for acute heart failure if cut-offs are adjusted for renal function, for example the level of BrainNP to 200 pg/mL if GFR < 60 mL/min/1.73 m².

Thus, cardiac disease is near universal in patients with renal failure and the presence of one or more of the above echocardiographic signs does not predict prognosis. However, LV dysfunction, as well as LV hypertrophy, are strong predictors of outcome, with improved outcomes shown for regression of echocardiographic hypertrophy. Furthermore, several other indices, such as RV function, pulmonary hypertension, and calcific valvular disease, significantly impact prognosis. Nevertheless, no clear guidance exists as to the frequency of follow-up echocardiography in patients with renal disease. ■

Symposium 9
Uremic cardiomyopathy
Sunday, 11.45 – 13.15, HALL F

Cardiac comorbidity in patients with renal disease is enormous, and many common diseases like hypertension and diabetes affect both the heart and the kidney. Cardiac disease is also the most common cause of death in patients with renal disease (as it is for the population in general). Vice versa, renal disease measured as reduction in glomerular filtration rate (GFR) is a powerful, well-established prognosticator of cardiovascular morbidity and mortality even in populations at relatively low risk of cardiovascular disease.

Assessment of cardiac structure and function in chronic renal failure (CRF) is largely based on echocardiography, due to the risks associated with contrast application for both computed tomography and magnetic resonance imaging. Biomarkers such as troponin and natriuretic peptides (NP) supplement information from cardiac imaging. The most important changes in structure and function associated with CRF are discussed below; more than half of patients initiating dialysis treatment have three or more of these features and nearly 90% at least one.

Left-ventricular (LV) hypertrophy and remodeling due to hypertension. There is a clear prognostic impact of the pattern of cardiac remodeling, with concentric hypertrophy having the worst prognosis. Unfortunately, there is no pattern-specific therapy for hypertension, although some data suggest better regression of LV hypertrophy under angi-

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Gert Mayer
President of the 53rd ERA-EDTA Congress in Vienna



Danilo Fliser
Chair of the Scientific Committee of the Vienna Congress

Management of Hyperkalemia: Challenges and Considerations in Patients with CKD

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

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

Purpose of Activity

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

Educational Objectives

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

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

Agenda/Faculty

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

PHYSICIAN ACCREDITATION STATEMENT

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

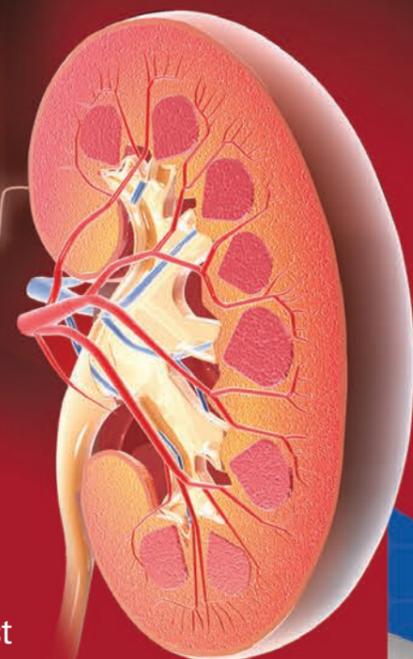
Target Audience

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

This symposium is funded by AstraZeneca



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





FABIO PAGLIALONGA
Milan, Italy

Optimizing blood pressure control in pediatric CKD and dialysis patients

Hypertension (HTN) is common in pediatric patients with chronic kidney disease (CKD), according to different studies affecting 52-67% of children with CKD stages 2-4, 59-79% of those on chronic dialysis, and 56-93% of pediatric renal transplant recipients. Poor blood pressure (BP) control is associated with a more rapid progression of CKD in patients with CKD stages 2-4 and faster loss of residual renal function in children with end-stage renal disease (ESRD); even more importantly, HTN is associated with an increase of left-ventricular mass index and carotid intima-media thickness in this population.

The pathophysiology of HTN in children with CKD is complex and multifactorial. Volume overload and activation of the renin-angiotensin-aldosterone system (RAAS) have traditionally been considered as the main causes of HTN, but several other contributing factors can play a role, such as sympathetic overactivation, endothelial dysfunction, chronic hyperparathyroidism and drugs.

The first step to optimize BP control in children with CKD is an accurate BP assessment. Although office and home BP measurement are still recommended by different guidelines and widely used in the pediatric literature and in the clinical practice, only ambulatory BP monitoring (ABPM) can provide a comprehensive BP assessment. This is because it al-

lows the identification of children with masked HTN who are at increased risk of left-ventricular hypertrophy, white-coat HTN and nocturnal HTN. ABPM can also provide information about BP variability, the role of which has recently been demonstrated in cardiovascular morbidity in adults with CKD.

Based on the results of the ESCAPE trial, which showed an improved renal survival in children with CKD on a fixed dose of angiotensin-converting enzyme (ACE) inhibitor on intensified BP control (target BP < 50th percentile) compared with those on conventional control (BP from 50th to 90th percentile), it is generally accepted that target on-treatment BP for pediatric patients with CKD should be < 50th percentile. As regards patients on dialysis, most guidelines suggest a BP level < 95th percentile.

Given the multifactorial nature of HTN in children with CKD, the management of BP in this population is complex and several aspects should be taken into account, in particular fluid and sodium control, and antihypertensive medications. Volume control is essential for HTN prevention and treatment, particularly in children with ESRD, but it is hampered by difficulties in reaching an accurate assessment of the volume status in this population. The assessment of dry weight (DW) (i.e. the optimal weight of the patient at the end of the dialysis session) should rely not just on clinical judgment, which is grossly inadequate, but on a comprehensive evaluation, including bioimpedance analysis (BIA) and, for patients on hemodialysis (HD), blood volume monitoring (BVM). Both single-frequency and multifrequency BIA have proven useful to improve body composition assessment and cardiovascular status of children on dialysis in some reports.

Several studies demonstrated that the use of BVM in children on HD is associated with BP improvement, tailoring of antihypertensive medications and decreased dialysis-associated morbidity.

After identification of the correct DW, the dialysis prescription should be adapted to optimize volume control. As regards peritoneal dialysis (PD), fluid transport across the peritoneal membrane occurs through two main ways: a solute-free water transport through ultras-small pores (aquaporin-1 channels) driven by osmotic gradient, and a solute-coupled water transport, driven by osmotic and hydrostatic pressure gradient. To increase ultrafiltration during PD, short dwell times with relatively low fill volumes should be prescribed; possible alternatives are the use of icodextrin and higher dialysate glucose concentration, with its potential toxicity. As regards HD, a few strategies can be implemented during the sessions to facilitate fluid removal, such as sodium and ultrafiltration profiles or mannitol infusion, but the evidence supporting these methods is scanty. Convective therapies could have a role in improving ultrafiltration, but no studies have so far investigated this issue in children.

Reduction of interdialytic weight gain (IDWG) is critical for DW achievement, particularly in patients on HD. Higher IDWG is associated with higher left-ventricular mass index and poorer BP control in this population. Sodium control is essential in limiting thirst, reducing IDWG and decreasing BP in patients on dialysis. Given that compliance to hyposodic diet is absolutely low in pediatric patients, sodium removal during dialysis is of utmost importance. *(continued on page 14)*

Corticosteroid withdrawal in kidney transplantation

For many years, the immunosuppression protocols used in children receiving renal transplant included corticosteroids (CS), and apparently specific adverse drug-related effects of long-term exposure have been presented by several patients. Attempts to reduce this burden had to balance the expected clinical benefits against potential risks and disadvantages. The list of universal (age-independent) benefits includes improved glucose metabolism (expressed as lower incidence of post-transplant diabetes mellitus), better lipid profile (no statins needed), better blood pressure control (reduced incidence of hypotension), better (preserved) bone mineral density and fewer adverse cosmetic events. Better growth is a specific and very important target in paediatric patients. When immunosuppression is aimed at achieving these targets, the clinician must balance the expected benefits against the potential risk of more active production of donor-specific antibodies (DSA) and a higher incidence of acute / chronic rejection, resulting in poor long-term outcomes in terms of renal graft function and survival, as well as a higher risk of primary glomerular disease recurrence in steroid-free patients.

In recent decades, three major approaches to corticosteroid withdrawal (CW) have been reported: complete avoidance, early (< 7 days post-transplant) and late (>12 months) steroid withdrawal. The respective paediatric reports included single-centre and multicentre studies, as well as international randomised controlled trials (RCTs). It should be stressed that almost all trials included low-to-moderate immunologic risk patients. A variety of protocols were used, with the

basic rule that, in cases of early CW (or complete avoidance), induction was always a part of protocol (with different blocking or depleting antibodies), whereas no induction was necessary in cases of late CW (Fig. 1). In the vast majority of trials, tacrolimus (TAC) and mycophenolate mofetil (MMF) were used in maintenance immunosuppression, although TAC monotherapy was also reported (with depleting induction). The choice of induction type and the number of doses of the respective antibodies was determined by the duration of the pharmacodynamic effect of the specific biologic drug (Fig. 2) and also (in one trial) by including higher-risk patients (to depleting induction). The first general message coming from the major trials was optimistic in terms of safety data. There was no increased risk of acute and late acute biopsy-proven rejection (never > 14%; mostly about 10%), whatever the protocol used. The relevant meta-analysis confirmed no additional risk of acute rejection in steroid-free children. The reports from the studies, which included monitoring of anti-HLA antibodies, showed no detrimental effect of CW on the incidence and dynamics of post-transplant DSA production, which did not exceed 25% (in unsensitised recipients) and had no significant clinical relevance (at least in the short-term follow-up). The infection and post-transplant malignancy rates were reported to be comparable between steroid-maintenance and steroid-withdrawal groups. The only disadvantage may be the higher rate of post-transplant recurrence of primary glomerular disease (nephrotic syndrome), which was reported as the second cause of reintroducing steroids in steroid-free



RYSZARD GREUDA
Warsaw, Poland

children, so the underlying glomerular cause of renal failure may be regarded as an excluding entry criterion for CW, at least in some cases. The second general message from the major trials was that most patients were able to achieve several benefits, in terms of glucose tolerance, lipid profile, blood pressure control and development of metabolic syndrome, and this was not age-dependent. The significant growth benefit was achieved mainly by pre-pubertal children, who were the subgroup with the most benefits overall. It should be emphasised that there was no significant superiority of the one specific immunosuppression protocol over the others. Overall, the longer the effect of induction in avoidance / early withdrawal protocols, the more profound the reduction of concomitant drugs that was possible (in low immunological risk patients). Extended (> 6 months) blocking induction with daclizumab was used by the Stanford group to conduct a complete steroid avoidance trial (with no single dose of steroids – an approach that is currently not available due to disappearance of daclizumab from the market). Extended (up to 9-12 months) in terms of pharmacodynamic effect, depleting induction with alemtuzumab

New insights into iron metabolism and deficiency

Monday 23 May 2016

13:30–15:00

Hall B, Level 2

Austria Center Vienna

Chair: Professor Angel de Francisco

Co-Chair: Professor Kai-Uwe Eckardt

Programme

13:30 Lunch boxes will be provided

13:45–13:50 Chair's introduction
Angel de Francisco (*Santander, Spain*)

13:50–14:10 ID prevalence in patients with CKD – a matter of definition?
Kai-Uwe Eckardt (*Erlangen, Germany*)

14:10–14:30 Iron pathophysiology – its complexity and our knowledge gaps
Tomas Ganz (*Los Angeles, USA*)

14:30–14:50 Diagnosing and treating ID/IDA – meeting your patient's needs
Jolanta Małyszko (*Bialystok, Poland*)

14:50–15:00 Closing remarks and Q&A
Angel de Francisco

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Date of preparation: April 2016
CHZH/FER/16/0045a

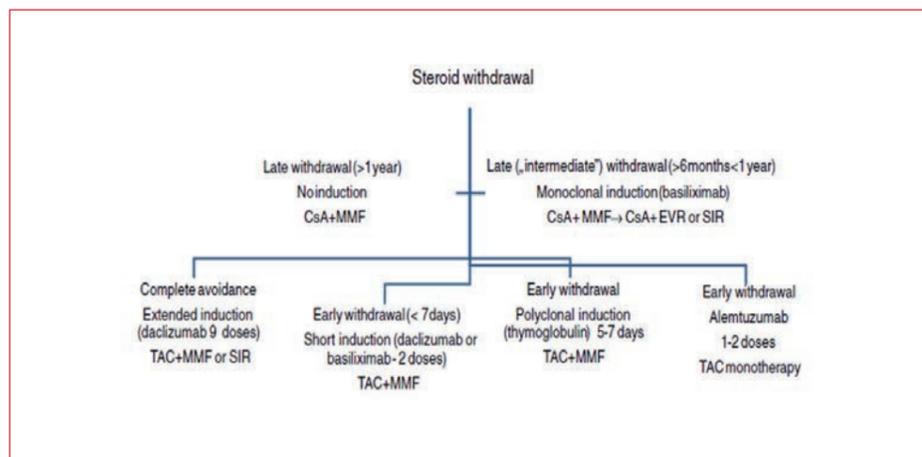


Figure 1: Summary of steroid minimization protocols in paediatric renal transplantation: complete avoidance, early and late withdrawal © Grenda

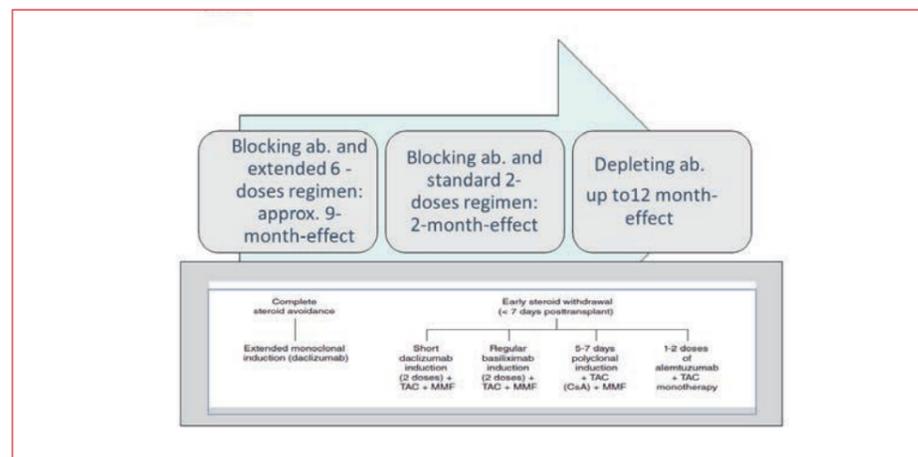


Figure 2: Variable duration of induction effect – important for selection of steroid withdrawal protocol © Grenda

allowed maintenance immunosuppression to be reduced to tacrolimus monotherapy in the Pittsburgh group experience. In other studies (like the TWIST trial), two doses of daclizumab allowed steroid withdrawal on day 5 post-transplant, and the combination of TAC+MMF was then maintained as stable long-term immunosuppression. Many paediatric transplant centres worldwide currently apply the TWIST protocol (anti-IL2R+ TAC+MMF + CS < day 5) with one modification, namely substitution of two doses of daclizumab (no longer available) by two doses of basiliximab. The optimistic report on early steroid withdrawal in patients at higher immunological risk, using high-dose polyclonal depleting induction (thymoglobuline) of 9 mg / kg / therapy (Stanford group) shows that the idea of steroid minimisation might be extended to a wider population of paediatric renal graft recipients.

Late steroid withdrawal with no induction is based on triple immunosuppression conducted within at least one year and

then – based on stable and good renal function (and / or additionally on a normal result of the protocol renal biopsy) – withdrawal of steroids. This approach has also proven similar efficacy and safety to early withdrawal protocol, with patients 'losing' a year of being on steroids. As the positive effect of CW on growth is mainly expressed in young, pre-pubertal children, the rationale of such delay should be discussed. On the other hand, the use of (depleting) induction in EBV-seronegative young children (>50 % below 10 years of age) is a risk factor for further post-transplant lymphoproliferative disease (PTLD), so careful evaluation of benefit / risk ratio must be done before a decision is taken on the individual CW approach.

In summary: steroid withdrawal in paediatric kidney transplantation is currently regarded as a proven safe and effective procedure in low immunological risk patients, provided that all the individual pro's and contra's are carefully evalu-

ated. Using high-dose polyclonal induction may extend this policy to patients at higher immunological risk, but long-term evaluation of this approach is still required. ■

References

1. Grenda R et al. , Am J Transplant. 2010; 10(4): 828-836
2. Höcker B et al., Nephrol Dial Transplant 2010; 25: 617-624
3. Grenda R, Pediatr Nephrol 2013; 28: 2107-2112

Symposium 14
Dialysis and transplantation in children
Sunday, 15.15 – 16.45, HALL F



MARIAN KLINGER
Wrocław, Poland

How can we diminish long-term renal allograft loss?

Addressing organ quality, HLA-antigen matching and comorbidities

The survival of renal transplant recipients is slowly but continuously improving, despite the growing number of elderly patients and the increase in kidney allografts harvested from extended-criteria deceased donors. The last ERA-EDTA registry reports five-year patient survival of 85% for the cohort transplanted in 2005-2009 compared with slightly below 70% in 1990-1995. This improvement extends up to 10 years, with a survival rate of 60% for transplantation in 2000-2005 versus 40% for years 1990-1995. The data from European Collaborative Transplant Study (CTS), encompassing about 150,000 renal transplant recipients (1990-2014) from deceased donors, shows 55% 10-year kidney allograft, and 70% death-censored kidney allograft survival, indicating that death of recipients with a functioning graft is an important cause of allograft loss.

The statistics from CTS depict simultaneously the significance of organ quality and HLA-antigen matching for long-term patient and renal allograft survival. Ten-year survival of recipients of kidneys from living-related donors reached 90%, with the same 90% rate of graft functioning for a transplant from haploidentical siblings, and with a rate of 75% for kidneys from one haplotype-matched living-related donors.

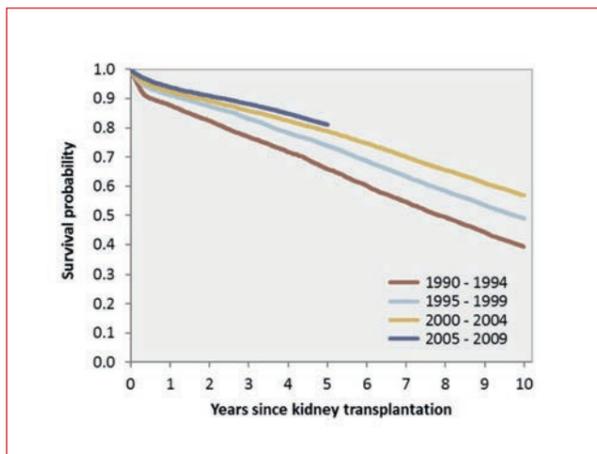


Figure 1: Patient survival after first kidney transplantation by cohort © ERA-EDTA Registry (slides summarizing Annual Report 2013, available at www.era-edta-reg.org)

Analyses included data from the following countries and regions: Austria, Belgium (French speaking part), Denmark, Finland, Greece, Iceland, The Netherlands, Norway, Andalusia (Spain), and Scotland (UK). Survival probabilities were adjusted for fixed values for age (60 years), gender (60% men), and the primary renal disease distribution (20% diabetes mellitus, 17% hypertension / renal vascular disease, 15% glomerulonephritis and 48% other primary renal disease).

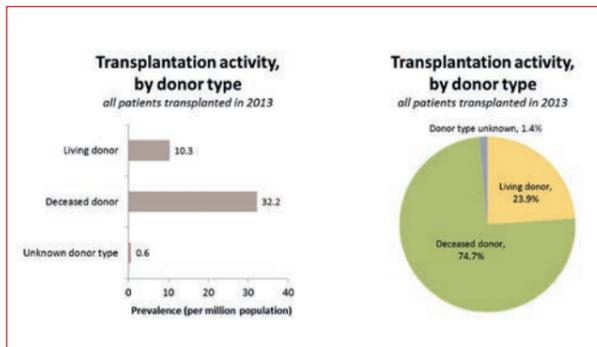


Figure 2: Renal transplants performed in 2013 by donor type © ERA-EDTA Registry (slides summarizing Annual Report 2013, available at www.era-edta-reg.org)

There are a few ways to improve organ quality. The first approach is a more intensive living donation program, with promotion and implementation of paired kidney exchange. The participation of living donors in European transplant activity in 2013 was 23.8% (ERA-EDTA Registry) whereas, for instance, in the UK the percentage was 35.8% and in the Netherlands 55% – clearly illustrating the existing reserves.

The other path is to improve organ quality from deceased donors by shortening cold ischemia time. It is documented that, compared to cold ischemia category of 0-10 hours, 6-year graft survival was progressively worse for 11-20 hours, 21-30 hours and, significantly, for >30 hours. Some observations show that, compared to cold storage, machine perfusion may positively influence graft survival with cold ischemia time > 24 hours or derived from extended criteria deceased donors.

The ultimate goal of renal transplantation is the achievement of recipient survival as close as possible to that of peers from the general population, with one transplant serving for life. In the situation of organ shortage the allocation policy is subordinated to fulfillment this task. For that reason, Eurotransplant implemented with success the senior program, in which kidneys of elderly donors (≥ 65 years) are allocated to recipients aged ≥ 65 years.

Long-term observations point out the near equal risk of graft loss due to recipient death and due to graft failure with return to dialysis. The most frequent cause of recipient death is cardiovascular complications, followed by infections and malignancy. Cardiovascular comorbidities frequently have their onset even before the dialysis period. Therefore, an important part of transplant care is the prevention of obesity, metabolic syndrome, the reduction of the frequency of glucose metabolism disorders, the appropriate treatment of new-onset diabetes mellitus (appearing in at least 20% of patients), and dyslipidemia. The common comorbidity in renal transplant recipients is hypertension, which ranges from 50% to 80% in adult recipients. There is some evidence that renin-angiotensin-aldosterone system blockade is associated with better patient and graft survival.

It is currently recognized that chronic allograft damage is basically produced by insufficient immunosuppression with chronic antibody-mediated rejection as the principal cause of the graft loss. Protocol surveillance biopsies and de novo donor-specific antibodies (DSA) measurement are essential tools for revealing deficiency in the effectiveness of the immunosuppressive regimen. The role of immune monitoring and immunosuppression tailored to the strength of the alloresponse is rapidly developing. Recent studies suggest that the particular clinical threat is associated with appearance of C1q-binding donor-specific anti-HLA antibodies and with the occurrence of antibodies directed against HLA-DQ antigens. The other validated assay is T-cell ELISPOT, which measures alloantigen-specific donor T-cell responsiveness as an estimate of immunological risk.

Nonadherence to immunosuppressive drugs is the other important factor significantly compromising graft survival. It is estimated to occur in one fifth of kidney transplant recipients.

The subject of constant debate is the potential benefits from calcineurin inhibitor-free regimens. Belatacept, a second-generation, higher avidity variant of CTLA4lg (abatacept), was approved by the Food and Drug Administration for prophylaxis of transplant rejection in 2011. Long-term follow-up of recipients on belatacept has demonstrated superior glomerular filtration rates as compared with calcineurin inhibitors, albeit with an increased risk of early and histologically se-

vere rejection. The significantly higher costs of belatacept are an obstacle for its wider application in low immunological-risk recipients. ■

References

1. ERA-EDTA Registry Annual Report 2013, published July 2015
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3. Pratschke J, et al. *Transplant Rev* 2016; 30(2): 77-84

Symposium 13

Lingering issues in kidney transplantation
Sunday, 15.15 - 16.45, HALL E

(continued from page 12) Sodium removal during PD occurs through small pores and it depends on the diffusive sodium gradient, the peritoneal surface area recruitment, and the dwell time, with large volumes and long dwells favoring sodium removal. In HD, sodium is mainly removed by convection (ultrafiltration), while the contribution of diffusion is often negligible, due to the usually low plasma sodium concentration of the patient at the beginning of HD. An individualized dialysate sodium prescription could optimize sodium removal, but the high preHD serum sodium variability makes this strategy difficult to implement in clinical practice.

Some dialytic strategies can optimize both fluid and sodium management. Adapted PD consists of two sequences of dialysis, with some exchanges of short dwells with low dwell volumes to promote ultrafiltration followed by exchanges of longer dwells with larger dwell volumes to increase sodium removal. A pilot study in adults showed a significant positive effect of this PD modality on BP control. As regards HD, intensified HD regimens (daily HD, hemodiafiltration, nocturnal HD) have been associated in adult and pediatric patients with a lot of clinical benefits, including better BP control.

As far as antihypertensive medications are concerned, agents that act on the RAAS are currently recommended as first-line agents for HTN in pediatric patients with CKD. This approach is based on the possible beneficial effect of RAAS antagonist on CKD progression. It is supported by some pediatric studies, which showed a better BP control and a lower prevalence of left-ventricular hypertrophy in children with CKD treated with this class of drugs as compared with those treated with other antihypertensive medications.

Notwithstanding the advances in the understanding of the etiopathogenesis of HTN, BP control remains suboptimal in the majority of patients. Given that HTN remains a leading risk factor for cardiovascular disease in children with CKD and cardiovascular disease is the first cause of death in patients starting with CKD in the pediatric age group, more effort will be needed in the future to manage this problem, in order to improve the long-term outcome of children with CKD. ■

Symposium 14

Dialysis and transplantation in children
Sunday, 15.15 - 16.45, HALL F



JAMES HEAF
Copenhagen, Denmark

The treatment of the patient presenting with acute uremia by peritoneal dialysis (PD) was very common in former times. A stiff catheter using an 'acute stick' was used, inserted using the blind Seldinger technique. The technique went out of fashion in the 21st century, being replaced by the use of a central venous catheter (CVC) and acute hemodialysis (HD). The question arises whether this was wise. Acute CVCs are associated with an increased risk of acute mortality of 3% due to a high risk of bacteremia. Departmental inertia also reduces the chances of the patient subsequently being offered dialysis choices other than facility HD. Urgent PD can thus be expected to increase PD prevalence. PD therapy offers many advantages to facility HD. Studies suggest an increased patient survival relative to HD during the first 2-3 years, possibly due to better preservation of residual renal function. It provides better rehabilitation, independence from hospital treatment and improved travel opportunities. It is also more economical.

Unplanned start of dialysis is still a major problem, affecting 36-49% of patients. The ideal situation would be to avoid the requirement for urgent dialysis, and predialysis planning should be optimized with this end in view. Many factors contribute to the high incidence of urgent dialysis in most centers: acute uremia, acute exacerbations of chronic uremia, late referral, patient noncompliance, access com-

'PD first' as the standard of care?

The demise of urgent PD was unplanned and not evidence based

plications and delayed planning. Some patients experience rapid clinical deterioration despite unremarkable biochemistry. Urgent PD is also appropriate for acute kidney injury (AKI) patients, where a metaanalysis has shown noninferiority to blood purification techniques. A randomized controlled study of AKI patients has shown identical efficacy to daily HD, without any risk of hyperkalemia. Contraindications to PD include recent abdominal surgery, other abdominal problems, and life-threatening conditions such as pulmonary edema and severe hyperkalemia. A prior choice of PD maintenance therapy by the patient is advantageous, but not mandatory.

Many studies have been performed, comparing urgent PD with planned PD or urgent HD. Most use placement of a tunneled Tenchoff catheter within 24 hours of admission by a dedicated nephrologist or surgeon. Subsequently, the patient is treated by low volume PD (1000-1200 ml per dwell) in the supine position, often using automated PD (APD) with a low tidal volume (50-75%). The treatment can be repeated (for example, 20l thrice weekly) until PD training can be started after three weeks.

The results are encouraging, with no increased risk of leakage, hernias or infections. Two studies have reported an increased risk of mechanical problems, particularly catheter displacement, with subsequent catheter loss. A recent randomized controlled trial suggests that use of the self-locating tungsten catheter solves this problem. One study found an increased risk of technique failure, mainly due to mechanical problems. However, the difference in technique failure rate between early start (6% at 6 months) and late start (2%) is not clinically important. Continuous ambulatory PD (CAPD) is usually regarded as contraindicated for urgent PD, due to an increased risk of leaks. However, studies using insertion through the rectus muscle and the applica-

tion of purse string sutures to the catheter during the operation show that CAPD is possible, permitting early patient training and rapid discharge to outpatient treatment. A successful urgent PD program requires considerable logistics. A policy decision will be needed to make PD the priority dialysis treatment for urgent patients. The department should be experienced in PD, preferably with a dedicated PD physician. Ward nurses will need PD training, since PD expertise is often confined to the outpatient PD training clinic. Since the practical problems of urgent PD are often different from those of maintenance PD, a prespecified PD prescription regimen should be developed. Most importantly, a nephrologist or surgeon, preferably dedicated to PD catheter placement, should be able to place a catheter within 24 hours. The development of an assisted PD home dialysis program would be an advantage, since some patients started on urgent PD will later be found to be unable to perform independent PD due to mental or somatic disorders. In conclusion, the demise of urgent PD was unplanned and not evidence based. The introduction of an urgent PD program will reduce the incidence of bacteremia and may reduce mortality. Patient choice may be improved, and PD prevalence increased. ■

Symposium 8
Should PD as initial dialysis modality become the standard of care?
Sunday, 11.45 - 13.15, HALL E



MARKUS PIRKLBAUER
Innsbruck, Austria

Cardiovascular (CV) events are the leading cause of death among chronic kidney disease (CKD) patients. While coronary artery disease is most prevalent in the general and early CKD population, CV mortality becomes mainly driven by congestive heart failure and sudden cardiac death at later CKD stages. Accordingly, the predictive value of classic CV (Framingham) risk factors such as hypertension, hyperlipidemia and adipositas declines during CKD progression towards ESRD, whereas other risk factors, such as volume overload, anaemia, malnutrition, chronic inflammation and vascular calcification become more important. The latter is a common complication in HD patients and is causally related to disorders of mineral and bone metabolism (CKD-MBD).

Both disturbances of phosphate homeostasis and the administration of excessive calcium (either via calcium containing phosphate binders or a high dialysate calcium concentration) are involved in the development of vascular calcifications in the HD population. In this regard, a large meta-analysis recently demonstrated a mortality reduction of 13% in HD patients using calcium-free compared to calcium-containing phosphate binders. HD patients with low turnover bone

The rapidly exchangeable calcium pool in hemodialysis patients

disease seem to be especially susceptible to the harmful effects of calcium loading, although the correlation between bone turnover and vascular calcification is not absolute. Current KDIGO guidelines generally suggest a dialysate calcium concentration of 2.5 mEq/l for most HD patients to avoid a positive calcium mass balance. This recommendation is based on relatively stable intradialytic serum calcium levels using this dialysate calcium concentration (dCa). However, several investigators have clearly demonstrated that calcium burden is hardly associated with serum calcium levels and that we regularly underestimate the amount of calcium that is transferred into chronic HD patients during each HD ses-

sion using a dCa of 2.5 mEq/l, despite relatively stable serum calcium levels. In line with this finding, high calcium intake but not steady-state serum calcium concentration has been demonstrated to correlate with coronary calcification in young HD patients.

Since the description of the calcium-sensing receptor by Brown and Hebert in 1993, our understanding of serum calcium regulation has improved substantially. Via dose-dependent effects on kidney, bone and the intestine, parathyroid hormone (PTH) and active vitamin D regulate and synchronise these calcium-regulating organs (*continued on page 16*)

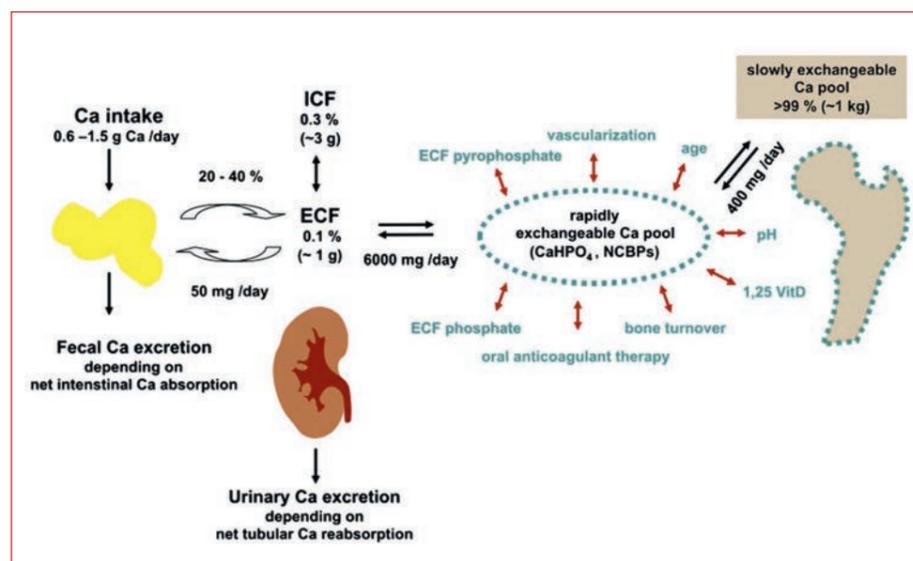


Figure 1: Calcium homeostasis and factors influencing the rapid exchangeable calcium pool © Pirklbauer M et.al. NDT2011; 26(8): 2438-44

Uremic toxins: their role in CKD-MBD

Chronic kidney disease, bone remodeling and cardiovascular calcification

Chronic kidney disease (CKD) is associated with all the components of chronic kidney disease-associated mineral and bone disorder (CKD-MBD), particularly cardiovascular calcification and abnormal bone remodeling. In early CKD stages, abnormalities of bone structure and function appear mainly to reflect the presence of adynamic bone disease in a significant proportion of patients. This low-bone-turnover disease may be related to a predominant action of bone metabolism-inhibitory substances that induce a resistance state to stimulatory agents such as that reported for parathyroid hormone (PTH). The development of high-turnover bone disease occurs only later, when serum PTH levels are able to overcome peripheral PTH resistance induced by inhibitory factors of bone remodeling.

of the bone. Accordingly, in an analogy to bone remodeling, we and others have described the concept of vascular remodeling; it is noteworthy that there is increasing evidence for a close relationship between abnormal bone and abnormal blood vessel function

The uremic syndrome is a complex condition of numerous organ dysfunctions. It is attributable to the retention of uremic toxins, a myriad of compounds that under normal conditions are excreted by healthy kidneys. These toxins can be subdivided into a family of three groups of molecules: (1) small, water-soluble molecules, (2) so-called "middle molecules", and (3) protein-bound molecules. Most have been shown to be associated with one or more complications of CKD at different

levels, and many contribute particularly to the development of both cardiovascular disease and CKD-MBD.

Uremic toxins may play a central role in the crosstalk between bone and the vascular system. They are generated by an increase in production and a decrease in elimination in patients with CKD (Figure). Essentially, the role of uremic toxins in cardiovascular outcomes and CKD-MBD has been suggested based on epidemiologic and experimental studies.

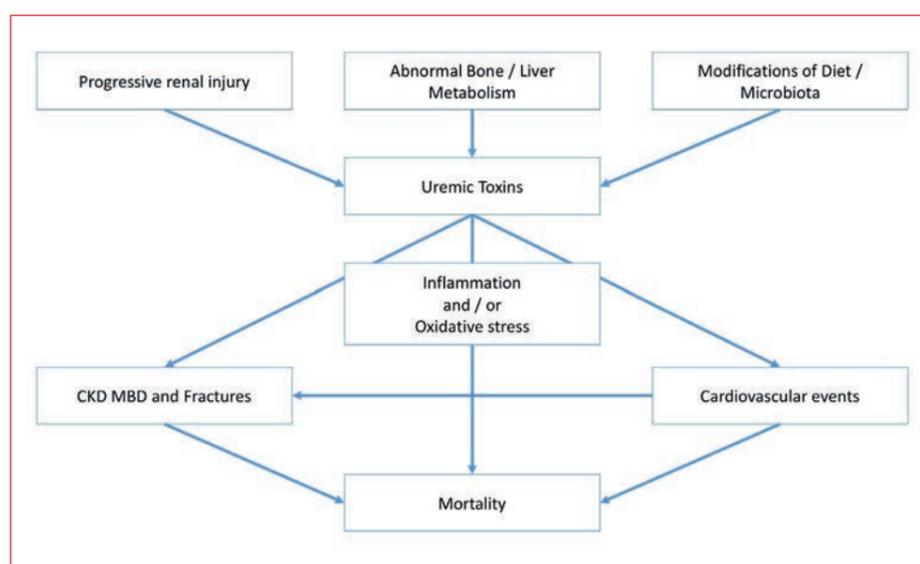


Figure 1 © Massy

Cardiovascular calcification in CKD has been recognized as an active, cell-mediated process of pathological mineralization of soft tissues that are normally protected from calcification, with similarities to the physiological mineralization

Numerous experimental studies have shown the accumulation of phosphate-induced cardiovascular abnormalities and altered bone remodeling, either directly or indirectly via, for instance, an increase in serum PTH and / or fibroblast growth

(continued from page 15) to maintain the individual mid- to long-term (i.e. steady-state) serum calcium concentration.

However, one fact that has mostly been neglected hitherto is that calcium enters the body rather rapidly after gastrointestinal uptake or during dialysis. Hence, as the total amount of calcium in the extracellular fluid (ECF) is low and the concentration is tightly regulated, just like in healthy individuals, mechanisms must be in place in HD subjects to either acutely excrete or at least to safely deposit calcium intermittently in order to avoid acute hypercalcaemia and thus potential impairment of various cellular functions. In this regard, some elegant animal studies have already demonstrated that acute serum calcium regulation (i.e. on a minute-to-minute basis) is primarily independent of calcitropic hormones (PTH, active vitamin D or calcitonin), cell-mediated bone remodelling, gastrointestinal uptake or renal calcium handling.

For example, a rapid counterregulatory response to acute hyper- and hypocalcaemia has been observed in rats within several minutes, that is still present after combined nephrectomy and thyro-parathyroidectomy. Administration of bisphosphonates did not alter this rapid counterregulatory response. Interestingly, the involvement of bone tissue in acute calcium regulation independently of cell-mediated remodeling was proposed in the 1970s but did not receive much attention until recently. Radiolabelled calcium perfusion experiments in dogs demonstrated calcium exchange fluxes of more than 6000 mg/day between extracellular fluid (ECF) and bone surface under physiological conditions. As this exceeds

many times the amount of calcium turnover by cell-mediated bone remodelling (approximately 500 mg/day), a rapidly exchangeable calcium pool (ECP), located at the bone surface, has been postulated. Accordingly, the ECP is thought to be in dynamic equilibrium with the ECF and might act as a temporary buffer, storing or liberating calcium in the event of acute calcium loading (e.g. as during dialysis or oral calcium load) or deprivation in order to counteract acute serum calcium deviations. Indeed, calcium mass balance analysis in HD patients has already corroborated this concept by showing that an ECP is required to close the gap between measured intradialytic calcium burden and observed changes in extracellular calcium levels, even at low dialysate calcium concentrations (i.e. 2.5 mEq/l).

To this end, ECP function is thought to depend on physicochemical mechanisms involving amorphous calcium phosphate salts (e.g. brushite / CaHPO₄) with the highest solubility of all bone constituents, that convert into hydroxyapatite (HA) over time, potentially leading to a reduced calcium buffer capacity in the ageing bone. However, this conversion is prevented – at least in part – by active bone turnover and the presence of so called non-collagenous bone proteins (NCBPs; e.g. Osteonectin, Osteocalcin), directly bound to HA at bone surfaces. In addition to its calcium buffering capacity, the bone ECP might serve as barrier between the highly insoluble hydroxyapatite and the extracellular fluid, which is oversaturated with respect to calcium, thereby decreasing the calcium gradient towards bone and preventing a non-physiological drop in ECF calcium concentration.



ZIAD A. MASSY
Paris, France

factor 23. Other pathways for the indirect actions of uremic toxins include an induction of inflammation or oxidative stress (Figure). Several observational and experimental studies have demonstrated an association of excessive indoxyl sulfate levels with abnormalities of the cardiovascular system and bone turnover in CKD. Epidemiological studies have also shown a link between several uremic toxins and mortality in patients with CKD. These observations favor experimental and clinical attempts to modulate circulating levels of uremic toxins. To date, however, the different clinical approaches chosen to reach this goal have not been sufficiently powerful to improve patient outcomes.

In conclusion, uremic toxins appear to play an important role in the crosstalk between the diseased kidney and CKD-MBD. Further studies are needed to prove the hypothesis of a causal relationship, with appropriate therapeutic consequences. ■

Symposium 18
Bone, calcium and PTH in CKD
Sunday, 17.00 – 18.30, HALL F

During progression towards end-stage renal disease, both CKD-related and unrelated factors can potentially affect ECP function (see Fig. 1). For example, elegant labelling studies have demonstrated a link between phosphate levels and ECP size / accessibility by showing that hyperphosphatemia-induced hypocalcaemia is not due to calcium / phosphate precipitation in the ECF but is caused, rather, by a reduction of calcium efflux from bone.

This observation is also an attractive explanation for the decrease in serum calcium levels in CKD with hyperphosphatemia independent of changes in active vitamin D status. It is tempting to speculate that a loss of bone ECP capacity in some HD patients might lead to short-lasting episodes of serum calcium levels above the individual mid to long-term setpoint during HD or after ingestion of calcium containing phosphate binders. The resulting intermittent individual 'hypercalcaemia' (which may well involve values within the 'normal' reference range of a population, nevertheless) could partially explain the propensity of HD patients to develop soft tissue and vascular calcifications, especially in the event of calcium loading. ■

Symposium 18
Bone, calcium and PTH in CKD
Sunday, 17.00 – 18.30, HALL F

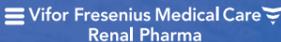
Protecting heart, vessels and bone – new ways to control phosphorus and potassium

Sunday 22 May 2016
13:30–15:00
 Hall E, Level 0
 Austria Center Vienna

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

Programme

- 13:30** Lunch boxes will be provided
- 13:45–13:50** Chairs' introduction
 Marcus Ketteler (Coburg, Germany)
 Alexander Rosenkranz (Graz, Austria)
- 13:50–14:10** Hyperphosphataemia – understanding the challenges
 Laurent Juillard (Lyon, France)
- 14:10–14:30** Advances in the management of hyperphosphataemia
 Philip Kalra (Manchester, UK)
- 14:30–14:50** A new approach in potassium management – can we change the treatment paradigm?
 Matthew R. Weir (Maryland, USA)
- 14:50–15:00** Closing remarks and Q&A
 Marcus Ketteler, Alexander Rosenkranz

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Date of preparation: April 2016
 CHZH/VEL/16/0046a



CHRISTIAN KURTS
 Bonn, Germany

The role of regulatory T cells in crescentic glomerulonephritis

Chronic kidney disease, bone remodeling and cardiovascular calcification

Regulatory T cells (Treg) have long been known to delay the progression of many immune-mediated diseases, including crescentic glomerulonephritis¹. We made two surprising observations that shed new light on Treg in kidney disease while studying the role of 1) CD103+ DCs and 2) the NFκB

component IKK2 in nephrotoxic nephritis (NTN), a dendritic cell-dependent murine model of human crescentic glomerulonephritis.

response and disease symptoms. This resulted from the loss of regulatory T cells (Treg) (Fig. 1). Thus, although IKK2 inhibition can suppress the induction of nephritogenic immune responses in vivo, it may aggravate such responses in clinically relevant situations, because it also impairs Treg and thereby unleashes pre-existing nephritogenic responses³.

In conclusion, our findings identify CD103+ DCs and IKK2 as important control elements for renal Treg and identify potential targets of future therapeutic strategies. ■

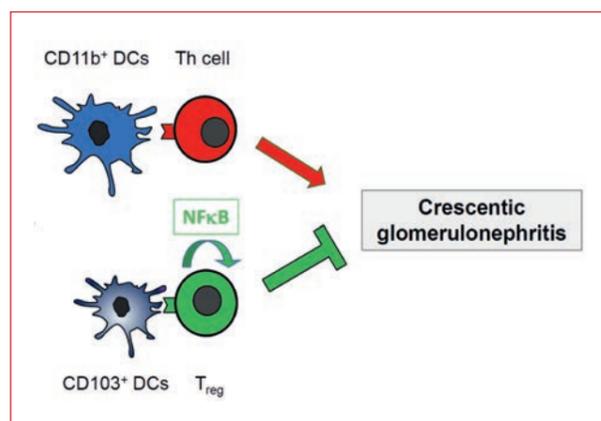


Figure 1: Role of CD103+ DCs and NFκB signaling in NTN. Proinflammatory CD11b+ DCs drive NTN through nephritogenic T helper cells, anti-inflammatory CD103+ DCs attenuate NTN through Tregs that depend on the NFκB component IKK2 © Kurts

1) The widely studied CD11b+ dendritic cells (DCs) promote NTN by stimulating nephritogenic T helper cells and constitute 95 % of all kidney DCs². The role of the small subset of CD103+ DCs is unknown. We removed these DCs using a number of genetic tools: Mice lacking the transcription factor Batf3 and the cytokine Flt3L and mice expressing the diphtheria toxin receptor under the Langerin promoter that is active in 50 % of renal CD103+ DCs. Whenever CD103+ DCs were less abundant, intrarenal Tregs were reduced as well. Conversely, Flt3L supplementation increased CD103+ DCs and Tregs, but also proinflammatory CD11b+ DCs to some degree. When the latter were removed by CCR2-specific antibodies, Flt3L supplementation ameliorated NTN. Taken together, these findings show that CD103+ DCs foster intrarenal Treg, thereby antagonizing proinflammatory CD11b+ DCs (Fig. 1), suggesting that strategies to increase CD103+ DC numbers or functionality might be advantageous in NTN.

2) NFκB inhibitors suppress DC maturation and are widely used to prevent immune-mediated diseases. We hypothesized that inhibiting the NFκB component IKK2 should attenuate NTN progression. Prophylactic pharmacological IKK2 inhibition indeed reduced DC activation and ameliorated glomerulonephritis in mice. However, therapeutic IKK2 inhibition during ongoing disease, which is relevant for clinical situations, unexpectedly aggravated the nephritogenic immune

References

1. Wolf D et al. J Am Soc Nephrol 2005; 16: 1360-1370
2. Kurts C et al. Nat Rev Immunol 2013; 13: 738-753
3. Gotot J et al. J Am Soc Nephrol 2015. [Epub ahead of print]

Symposium 17
Immunology and the kidney
Sunday, 17.00 – 18.30, HALL E



PIERRE RONCO
Paris, France

Membranous nephropathy (MN), a major cause of the nephrotic syndrome and chronic renal insufficiency, is an immune-mediated disease characterized by the accumulation of immune deposits on the outer aspect of the glomerular basement membrane. In experimental models of MN, it was shown that the accumulation of immune deposits could be initiated by in situ formation of immune complexes with the 'nephritogenic' antigen being either an endogenous component of the podocyte membrane or an exogenous antigen planted in the subepithelial space. The immune complexes stimulate assembly of the complement C5b-9 attack complex which is responsible for functional impairment of the glomerular capillary wall causing proteinuria.

Since the identification of megalin (the antigen responsible for Heymann nephritis) by Kerjaschki and Farquhar in 1982, the antigens involved in human MN have remained elusive. In 2002, we identified the first human podocyte antigen, neutral endopeptidase (NEP), in a rare subset of patients born with neonatal MN (1). NEP is expressed on the surface of podocytes, is a main component of the proximal tubule brush border, and is present in very specific locations in a variety of organs, including the brain (being identical to enkephalinase), the lung, the liver and the hematopoietic system (being identical to CD10 and the Common Acute Lymphoblastic Leukemia Antigen).

We have thus described a new disease called 'maternal-fetal alloimmunization with antenatal MN', which results from maternal antibodies that cross the placenta, bind to fetal glomerular podocytes, and mediate antenatal renal disease. All immunized mothers studied so far failed to produce NEP and lacked NEP enzymatic activity because of truncating mutations of the MME gene located in exon 7 (detected in all mothers) and in exon 15 (detected only in the first reported mother who was compound heterozygous) (2). Five families with

Immunization in pregnancy leads to membranous nephropathy

the same mechanism of disease have been identified hitherto, all from different countries. Pedigree studies have shown that these families are unrelated, although a founder effect suggested by the same mutation in exon 7 is likely, and that NEP deficiency is a hereditary genetic defect with a recessive pattern of inheritance. Although gene mutations were detected in all the mothers who produced anti-NEP antibodies, expression of the renal disease was variable, being determined by the mother's antibody response. Maternal production of complement-fixing anti-NEP IgG1, which also inhibits NEP enzymatic activity, seems necessary for the disease to develop; if only non-complement-fixing anti-NEP IgG4 with a weak inhibitory potency was produced, then proteinuria did not result (3). Inhibition of NEP activity by anti-NEP IgG1 antibodies may alter the metabolism of a number of regulatory peptides and thus have an impact on glomerular haemodynamics, endothelial permeability, tubular function and podocyte lesions. Pathogenic antibodies are directed against two conformational epitopes formed by non-sequential residues on the NEP protein.

Because renal function usually improves markedly in postnatal life due to the short half-life of maternal IgG circulating in the neonate, it is highly likely that prevalence of NEP-related alloimmune MN is greatly underestimated. However, screening of families with the disease is very important for at least two reasons. First, antenatal and perinatal nephron loss may lead to chronic renal failure detected later in life, during adolescence, or early adulthood. Some of these patients will need renal replacement therapy, thus implying a substantial economic healthcare burden. Second, subsequent pregnancies are at high risk for the fetus. Anti-NEP antibodies should be carefully monitored before and during pregnancy by immunofluorescence or ELISA tests (not commercially available). Before pregnancy, we recommend anti-B cell therapy (rituximab) to decrease the titer of anti-NEP antibodies. During pregnancy, corticosteroids and plasma exchanges (ideally immunoadsorption) should be considered.

A diagnosis of maternal-fetal alloimmune glomerulopathy should be considered if unexplained renal manifestations are present during the antenatal period and at birth, if they improve or disappear within the first weeks of life even though they can reappear later, and if they increase in severity with

the reiteration of pregnancies. In families where this disease is suspected, one should (i) assess circulating anti-NEP antibodies in the mother and child, (ii) verify the absence of NEP in the mother's urine and granulocytes, and (iii) perform a genetic mutation screen to confirm genetic deficiency. Identification of families with MME mutation will help screen potential NEP-deficient mothers among female siblings. For rapid screening of mothers at risk, we have developed an indirect immunofluorescence test based on phylogenetic variations of NEP expression.

Our findings had substantial implications. First, they provided proof of concept that a podocyte antigen could serve as target for the formation of subepithelial immune deposits in humans also. This paved the way for the identification of another podocyte antigen in 2009, the M-type phospholipase A2 receptor (PLA2R), a transmembrane receptor belonging to the mannose receptor family, which is the first autoantigen identified in primary (idiopathic) MN in adults (4). Second, maternal-fetal alloimmunization with antenatal MN, which bears similarities with disease linked to Rhesus incompatibility, is the first organ disease caused by alloimmunization. Other examples have been reported since then, including rare forms of neonatal myasthenia (5). ■

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Symposium 24
Development and pregnancy
Monday, 08.00 – 09.30, HALL B



ONDREJ VIKLICKY
Prague, Czech Republic

Living-donor kidney transplantation represents the best option to treat end-stage renal disease. A significant proportion of potential living donors cannot donate a kidney to their potential recipients, who have donor-specific ABO or HLA antibodies. As a consequence, for many of those recipients a significant dialysis vintage is associated with higher morbidity and mortality. In the last two decades, in many transplant programs such incompatibility has no longer represented a barrier to successful living-donor kidney transplantation. Besides well-known protocols for desensitization, which eliminate or significantly decrease the

Realizing the benefits kidney paired donation

Larger registries may create more efficient programs

level of either hemagglutinins or antiHLA antibodies to allow transplantation, kidney paired donation (KPD) represents another elegant but logistically demanding option.

KPD occurs when two or more living-kidney donor / recipient pairs, who are not compatible with each other because the recipient has circulating HLA- and/or ABO antibodies against his/her own donor, exchange the kidneys in such a way that recipients receive compatible kidneys. KPD avoids the costs and complications of desensitization therapies for ABO-incompatible (ABOi) and HLA-incompatible living-donor kidney transplantation.

There are several possibilities on how a KPD program can be organized. The simplest one is to perform two-way paired donation between two or three incompatible pairs. To avoid the possibility that, after one donor has given a kidney to the other pair's recipient, that recipient's

co-registered donor will refuse donating a kidney in return, paired-donation transplantations should be performed simultaneously. This type of program (i.e. short-chains and simultaneous paired donation), which was originally implemented in the United States, Korea and Netherlands, has been shown to be successful and safe. Following this experience, an equally efficient program has been implemented in UK. Other European countries such as Spain, France, Italy, Czech Republic, Austria and Switzerland have already started programs or are pushing to implement efficient programs.

As an alternative to the Dutch model, the number of involved pairs may be increased by constructing a chain of organ exchanges that even involves a dozen of pairs. Since it is impractical to perform all the exchanges simultaneously, they are usually accomplished in clusters over time. Here, the donor at the end of each cluster of transplan-

A symposium sponsored by Bayer

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

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



Science For A Better Life

Bayer Pharma AG
Müllerstrasse 168
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Germany

Welcome and introduction

Chair: Hermann Haller (Germany)

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

Patrick Rossignol (France)

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

Peter Rossing (Denmark)

Summary and close

Hermann Haller

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

L.AT.MA.04.2016.4039

tations serves as a 'bridge donor' to extend the interrupted chain of transplantations at a later time.

The most controversial issue is whether paired donors can or should be trusted to donate a kidney after their own co-registered recipients have already received transplants. However, the possibility that after donation the co-registered recipient does not eventually receive a kidney is prevented by altruistic donation (i.e. non-directed donation to an unknown person for reasons of altruism). In fact, when altruistic donation initiates a chain of transplantations, each subsequent donor makes the donation only after the co-registered recipient has already received a transplant. At the end of such a chain, the last donor donates to most suitable recipient from the waiting list or serves as 'bridge donor' for the future transplantation segment.

It must be underlined that the benefit of starting such a long chain of kidney transplantations may drive strong motivation in any potential altruistic donor. This strategy is known as non-simultaneous extended altruistic donor chains (NEAD Chains). Unfortunately, altruistic donation is not allowed in many countries whereas in other countries altruistic donors are almost nonexistent. In contrast, altruistic donation has been successfully implemented in European countries such as the Netherlands (for short chains), the UK and Spain, as well as in the US.

It has been proven that the match rate of incompatible pairs increases with the size of the pool. Therefore, large national or even international registries may be needed to create efficient KPD programs. In US there are competitive nonprofit registries such as National Kidney Registry or the Alliance for Paired Donation, which run database and allocation programs to achieve better HLA matching while involving most available donor-recipients pairs, and

also some single-center KPD independent programs. The Alliance for Paired Donation has already performed an international exchange with Greece, and other international alliances are currently been organized within Europe between Spain, France and Italy. It must be mentioned however that, unfortunately, legislation prohibits KPD in some countries (for example, Germany), thus so far precluding the construction of Europe-wide registry.

There are several logistical problems in KPD programs. First, when different centers have been involved in the program, either the donor or his/her kidney must travel to the center where transplantation is to be performed. The latter case calls for strict cooperation and involvement of more centers in large KPD programs. In that case, the procured kidney may travel for several hours between coasts in US and theoretically between the US East Coast and Western Europe.

Acceptance of blood group-incompatible donors for patients with low to moderate antibody increases transplant rates in KPD programs. However, ABOi living-donor kidney transplantation programs have been carried out in conjunction with KPD in many countries and therefore it is concurrent to KPD. In fact, recipients of blood type O with a donor of blood type A, which is the most common combination, have a low chance of finding a match in the KPD pool compared to other recipients, and ABOi transplantation remains the most viable option for many of them. Highly sensitized recipients also have poor chances of finding a match on the KPD program. Clearly, blood type O recipients and those with broad antiHLA antibodies may benefit from a large KPD program where they may have a better chance of finding a match. Also other strategies can be employed in highly sensitized patients, such as the acceptable mismatch programs and desensitization strategies. Combination of all

above-mentioned approaches in KPD may further improve the chance for a match in smaller programs.

In the Institute for Clinical and Experimental Medicine in Prague (IKEM), the first KPD was realized as early as 2003, and a systematic KPD program using a computer algorithm was implemented in 2012. Until recently, 50 living-donor kidney transplantations from KPD program were performed including 3 altruistic donor-initiated chains. Since 2015 also ABOi transplantations are involved in KPD program in terms of achieving better HLA match. However, there is a critical need to participate in larger, European-founded KPD program allowing ABO- and HLA-compatible living-donor kidney transplantation. ■

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Symposium 20
How to handle the sensitized kidney transplant recipient
Monday, 08.00 – 09.30, HALL A



NICK SELBY
Nottingham, United Kingdom

The statistics surrounding acute kidney injury (AKI) are as stark as they are well known to nephrologists. In addition to its high incidence and very poor patient outcomes, it is the potential to improve AKI care that maybe has the most traction. Whilst research into novel therapies continues, it is glaringly apparent that we have no current pharmacotherapies for AKI. In tandem we are increasingly aware of studies, encompassing a variety of health care systems, that highlight systematic deficiencies in the basic medical care of AKI patients. Although the burden of AKI is clearly appreciated within nephrology and critical-care circles, the same is not necessarily true more widely. Knowledge and awareness levels are variable across other specialties, and the appreciation of kidney disease in the general population is also low; for example, early research suggests that only 51% of people know that their kidneys make urine. The approach to AKI in the general ward must therefore address and take account of these issues.

Strategies to tackle AKI differ from many other areas in nephrology. The majority of patients at risk and who sustain AKI are not cared for by specialist teams, but are distributed across all acute specialities in the hospital. Educational initiatives are therefore important, not just for healthcare professionals but also for patients, their carers and the general public. Almost two-thirds of AKI in hospitalized patients is present at the time of hospital admission; just one of the statistics that suggest an inclusive approach with primary care is required. In addition, the majority of AKI occurs in association with acute illness, especially in those more vulnerable patients with multiple long-term conditions. These observations suggest that it is essential to avoid an excessively organ-centric focus; rather AKI should be evaluated within an individual's overall treatment plan and its presence utilized as a clinical indicator, a syndrome that identifies patients at higher risk of adverse outcomes to whom additional attention can be directed in a holistic way.

Following the 2009 National Confidential Enquiry into Patient Outcome and Death into AKI [1] the UK has seen national initiatives, as well as many improvement and innova-

NETs, histones and necro-inflammation in kidney disease

Tissue injury and inflammation promote each other. But what are the molecular mechanisms underlying these bidirectional causalities? Immunity-related cell death involves complement activation or cytotoxic T cells. Conversely, cell death-related immunity involves dying cells releasing danger-associated molecular patterns (DAMPs) that trigger innate immunity via pattern recognition receptors (PRR). The recent discovery of numerous forms of regulated necrosis now gives rise to a new theory we call necroinflammation. Necroinflammation describes an auto-amplification loop

'Think Kidneys': the UK experience

Prevention and management of AKI in the general ward

tion activities at local and regional levels. In 2011, the UK Renal Association published AKI guidelines, shortly followed by a clinical practice guideline from the National Institute of Health and Care Excellence (NICE) [2]. Most significant, however, has been the partnership between NHS England and the UK Renal Registry to convene a national AKI program ('Think Kidneys', www.thinkkidneys.nhs.uk). Within a three-year tenure, its stated aim is to reduce avoidable harm caused by AKI. This program has given impetus to all aspects of AKI quality improvement, and encompasses a wide variety of stakeholders including both expert professionals and patients. Underneath a steering committee, the program is organized into a number of different workstreams that each focuses on a different element of the AKI pathway (risk, detection, education, intervention, commissioning, and national data collection). Crucially, this national direction is designed to provide strategy and resources, whilst at the same time encouraging and supporting local innovation.

Outputs from the Think Kidneys program include a National Patient Safety Alert that has required all hospitals in England to install a standardized AKI detection algorithm (based on KDIGO definitions) in their biochemistry laboratory information management systems (LIMS). From this, alerts are generated for serum creatinine changes that are consistent with AKI. Alongside such efforts to improve AKI recognition, centers are gaining experience with care bundles to improve delivery of AKI care in a systematic way, as well as commissioning tools designed to improve post-AKI follow up.

This recognition of AKI by policy makers and the commissioning system is just one example of how the Think Kidneys program has looked to shape policy. Additionally, the Think Kidneys program is laying the foundations for a national data registry that will prospectively measure the incidence and outcomes of AKI on a national level. A national AKI registry would be an extremely powerful tool for improvement, providing organizations with a way to benchmark their performance, which in itself can drive change; it will also allow measurement of the effect of organizational-level AKI interventions. Currently, laboratory data on AKI are being collected within such a framework; next steps include linkage with other databases, in particular those containing hospital episode statistics so that AKI episodes can be married up with patient outcomes.

A final consideration is that not only must appropriate tools be developed, but it is equally important that an improvement architecture exists to allow their effective implementation. This point was illustrated in a randomized controlled trial of

driven by necrosis and inflammation. The auto-amplification loop of necroinflammation is accelerated by immunity-related cell necrosis and cell necrosis-related immune activation. Necroinflammation can be initiated by a few necrotic cells that activate the innate immune system, which subsequently leads to necrosis of more cells triggering more inflammation in a process that may eventually lead to organ failure.

Inflammation-related forms of cell necrosis.

Inflammation can trigger certain forms of necrosis. For example, necroptosis is defined by the receptor-interacting protein kinase 3 (RIPK3)-mediated phosphorylation of mixed-lineage kinase domain-like protein (MLKL), which by unknown means leads to plasma membrane rupture. Numerous signaling events can trigger RIPK3 phosphorylation, especially a conformational change of RIPK1 that is linked to several cell surface receptors. Necroptosis is well described as killing parenchymal cells of all tissues, including renal tubular epithelial cells. Ferroptosis is characterised by a defined lipid peroxidation signature in oxylipidomics analysis, caused by a



e-alerts for AKI that failed to result in improved patient outcomes. However, the isolated introduction of the alert without any quality improvement framework and without guidance for those receiving the alert meant that no change in physician behavior resulted. The Tackling AKI study is a pragmatic trial adopting an alternative approach (www.tackling-aki.org). Within a cluster randomized stepped wedge design a complex intervention (AKI alert, care bundle and education package) is being tested across a range of UK hospitals, supported by quality improvement methodologies. This type of study may provide answers not just as to whether the intervention results in better patient care and improved outcomes, but also to inform the most effective ways in which AKI strategies can be implemented.

In the absence of specific AKI therapies, as clinicians we feel an obligation to address the variations in standards of AKI care that currently exist. To do so, there are a number of considerations but nephrologists are perfectly placed to take the lead in programs that seek change at an organizational level. Within this, it is important that the impact of new initiatives are measured; we must not simply aspire towards improved patient outcomes, but actually demonstrate effectiveness of strategies aimed at the prevention and management of AKI. ■

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Symposium 19
Special situations with need
for nephrology advice
Sunday, 17.00 – 18.30, HALL B



HANS-JOACHIM ANDERS
Munich, Germany

failure of glutathion-peroxidase 4 function. Ferroptosis involves a lack of glutathione, which may be induced by inhibition of the cellular Cys / Glu-antiporter System Xc-controlled by p53 via SLC7A11 or heat shock protein beta 1 (HSPB1). Ferroptosis can occur in any glutathione-depleted cell and has also been described in renal tubular epithelial cells. Mi-

AN UNWAVERING COMMITMENT TO THE TASK AT HAND

Treatment of Hepatitis C in Patients With Chronic Kidney Disease: Challenges and Opportunities

Sunday, 22 May 2016

18:45 – 19:45

Hall G, Level-2

CHAIR

Marcus Säemann

Associate Professor
Clinical Division of Nephrology
and Dialysis
Department of Medicine III
Medical University of Vienna
Vienna, Austria

FACULTY

Annette Bruchfeld

Associate Professor
Karolinska Institute
Department of Renal Medicine,
Karolinska University Hospital
Huddinge
Stockholm, Sweden

David Roth

Professor of Medicine
University of Miami
School of Medicine
Miami, Florida

HEPATITIS C IS A SERIOUS BURDEN THAT CAN HAVE DIRE CONSEQUENCES³

According to the World Health Organization, the human cost of hepatitis C–related liver diseases is staggering: it claims the lives of approximately 500,000 people per year.⁴ However, recent advances in care have led many to believe that elimination of hepatitis C is possible. MSD remains committed more than ever to providing innovative solutions for advancement of chronic hepatitis C treatment and to working towards the ultimate goal of hepatitis C elimination.

References: 1. US Food and Drug Administration Drug Approval Package. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&AppNo=202258&DrugName=VICTRELIS&ActiveIngred=BOCEPREVIR&SponsorApplicant=MERCK%20SHARP%20DOHME&ProductMktStatus=1&goto=Search.DrugDetails. Accessed April 1, 2016. 2. Drugs@FDA: FDA Approved Drug Products. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>. Accessed April 1, 2016. 3. World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection. April 2014. <http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/>. Accessed March 30, 2016. 4. World Health Organization. WHO Key Facts. Hepatitis C. <http://www.who.int/mediacentre/factsheets/fs164/en/>. Accessed March 30, 2016.



Sustained Virologic Responsibility

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tochondrial-permeability transition-mediated regulated necrosis (MPT-RN) is independent of ferroptosis and necroptosis, as it depends on cyclophilin D and may partially overlap with a PARP1-mediated pathway of regulated necrosis, previously referred to as parthanatos. Both MPT-RN and parthanatos pathways have been shown in renal cells, in particular. Pyroptosis is a consequence of inflammasome-driven caspase 4/5/11 activation. Concomitant caspase-1 activity induces mature IL-1 β and IL-18 secretion, rendering pyroptosis particularly immunogenic. Whether pyroptosis can occur in renal cells is currently unclear. NETosis is a controlled and often suicidal act of activated neutrophils which results in the formation of neutrophil extracellular traps (NET) consisting of expelled chromatin loaded with lysosomal and cytosolic proteases.

Cell necrosis-related inflammation and back to necrosis, role of histones.

Necrotic cells release DAMPs and alarmins from several intracellular compartments. While alarmins are a heterogeneous group of mediators with different pro-inflammatory activities, DAMPs alert the innate immune system via Toll-like receptors, NOD-like receptors/inflammasomes, and C-type lectin receptors. DAMPs released by dying cells activate the PRRs on infiltrating immune cells such as dendritic cells, macrophages, neutrophils and lymphocytes, and induce the expression and local release of numerous pro-inflammatory mediators. In particular, TNF α and IFN- γ can induce necroptosis via two distinct pathways. TNFR1 activation by TNF α or TRIF activation via TLRs affects the conformation of RIPK1, which induces the phosphorylation of RIPK3 and MLKL, whereas IFN- γ signals use a STAT3-protein kinase R-dependent pathway to induce necroptosis. TNF α and IL-8 can also induce NETosis in neutrophils. Extracellular histones play a key role in necroinflammation. NET formation and other forms of necrosis involve the release of histones, which

elicit cytotoxic effects on endothelial and other cells. Extracellular histones do not seem to kill cells via a specific surface receptor but due to their strong basic charge.

Necroinflammation in kidney diseases.

The concept of necroinflammation can explain a number of clinical phenomena. For example, when an ascending urinary tract infection reaches the kidney, host defence involves LPS/TLR4-mediated pathogen recognition and CXCL12-driven neutrophil recruitment, which can cause abscess formation and massive renal cell necrosis. Necrosis disrupts internal barriers and promotes pathogen spreading and urosepsis. Circulating bacterial endotoxin is a potent stimulus for cytokine release from monocytes and other immune and non-immune cells, which has been referred to as a cytokine storm. In this process, cytokine-induced NETosis and histone release can occur everywhere in the microvasculature, which is indicated by increased levels of histones in the circulation of septic patients. Circulating histones cause cytotoxic effects to endothelial cells and activate platelets, which implies disseminated intravascular coagulation, tissue hypoperfusion and organ dysfunction, e.g. of the lung, the intestine, the heart, and the kidneys.

Regulated tubule necrosis also occurs in post-ischemic or toxic AKI, delayed graft function or rhabdomyolysis. In these diseases, inflammation is an important accelerator of tubular injury. Oxalate crystal formation inside tubules induces RIPK3- and MLKL-dependent tubular cell death (Mulay...Anders. Nat Commun 2016), and the associated ATP release from dying tubular cells triggers NLRP3 inflammasome activation, IL-1 β -dependent renal inflammation, and renal failure in mice (Mulay...Anders. J Clin Invest 2013). RPGN is usually presented as necrotising and crescentic glomerulonephritis (GN), which are classical presentations of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, lupus ne-

phritis, anti-glomerular basement membrane (GBM) disease. For example, in experimental anti-GBM disease, neutrophils undergo NETosis inside the glomerular capillaries and it is the release of histones that induces glomerular endothelial cell necrosis (Kumar ...Anders, JASN 2015). This became obvious as either the specific inhibition of NETosis or the neutralization of extracellular histones abrogated crescentic GN. Similarly, NETs are also found in necrotic glomerular lesions in human renal vasculitis. Complement-mediated cytotoxicity is another trigger for glomerular necroinflammation.

Necroinflammation is a theory that combines several concepts of kidney injury. Necroinflammation is a serial event involving cell necrosis triggering inflammation and further regulated necrosis, and so on. If it not treated at an early stage, necroinflammation can lead to organ failure or even system inflammation and remote organ injury. According to the concept, this process can be abrogated either by anti-inflammatory agents or by cell death inhibitors. The concept remains to be validated in patients. ■

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Symposium 17
Immunology and the kidney
Sunday, 17.00 – 18.30, HALL E



HANNES OLAUSON
Cambridge, U.S.A.

New insights into the FGF23-Klotho axis

New data on the link with cardiovascular disease

er, the initial onset and gradually accelerating perturbation in FGF23-Klotho expression appear closely connected with development of cardiovascular disease.

Over the last couple of years, a direct link has been established between disturbances in the FGF23-Klotho axis and cardiovascular disease. In the heart, FGF23 can bind and activate FGFR4 in a Klotho-independent fashion, and directly contributes to left-ventricular hypertrophy, a prevalent manifestation and well-established cardiovascular risk factor in CKD. Furthermore, circulating Klotho derived from shedding of membrane-bound Klotho has been shown to inhibit vascular calcification by preventing precipitation of calcium and phosphate in vascular smooth muscle cells, and protect against left-ventricular hypertrophy by inhibiting indoxyl sulfate.

However, significant controversies remain regarding the presence of membrane-bound Klotho in the cardiovascular system and whether vascular tissue is a direct target of FGF23. While some studies have suggested that Klotho is locally expressed by vascular smooth muscle cells of human arteries, and protects against vascular calcification by mediating FGF23's inhibitory effects on matrix mineralization, other studies have failed to detect membrane-bound Klotho in the

Patients with chronic kidney disease (CKD) suffer from a high cardiovascular disease burden. The increased cardiovascular risk derives from a number of aggregating traditional and non-traditional risk factors. Among the non-traditional risk factors, hyperphosphatemia and the homeostatic mechanisms controlling phosphate metabolism have received particular attention over the last 15 years. Recent clinical and observational studies suggest that FGF23, a bone-derived hormone that regulates mineral metabolism, is linked to cardiovascular mortality as well as left-ventricular hypertrophy, atherosclerosis and endothelial dysfunction.

In the kidney, FGF23 binds and activates a complex of FGF-receptors and the co-receptor Klotho. Disruption of FGF23-Klotho signaling is an early hallmark of CKD, and involves reduced tissue levels of Klotho and a reciprocal rise in circulating FGF23. It is currently not established whether the rise in FGF23 precedes the loss of Klotho or vice versa. Howev-

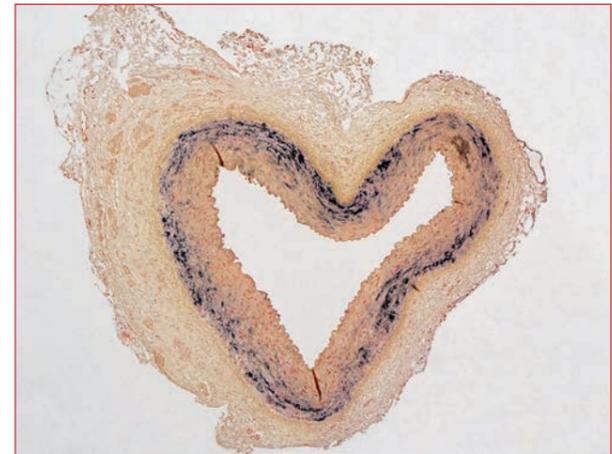


Figure 2: A von Kossa stained arterial biopsy from an end-stage renal disease patient undergoing living-donor transplantation reveals extensive calcification in the tunica media © Olauson

vascular wall. Also, a number of clinical studies have reported on a lack of association between serum FGF23 levels and degree of vascular calcification in patients with various extent of renal dysfunction.

In my talk I will highlight current evidence (or the lack thereof) for a role of FGF23-Klotho signaling in the development of uremic vascular calcification. Special attention will be directed to the expression of membrane-bound Klotho in the cardiovascular system, and potential explanations for the reported discrepancies will be discussed. Further, I will present novel data from a cohort with histopathologically scored vascular biopsies from over 140 ESRD patients undergoing living-donor transplantation, in which we have measured serum levels of FGF23 and Klotho. ■

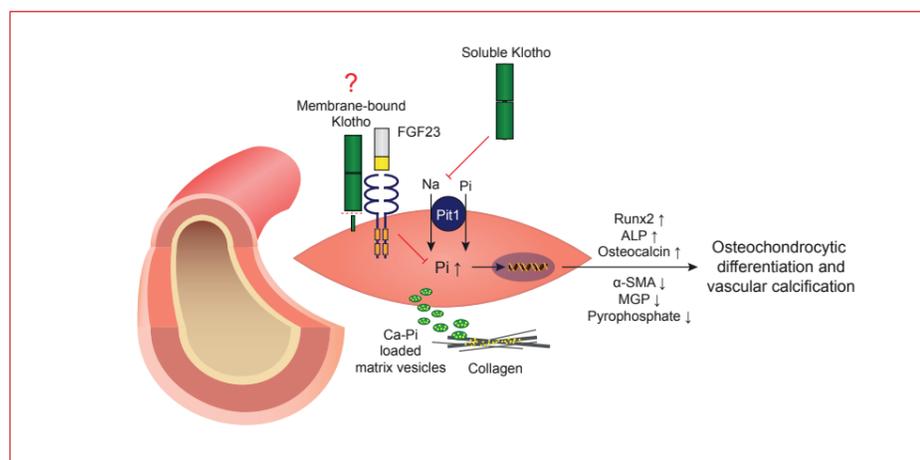


Figure 1: Schematic illustration of the vascular calcification process, and potential roles for FGF23 and Klotho © Olauson

Symposium 21
Calcification and calciphylaxis
Monday, 08.00 – 09.30, HALL D

Calcification in heart valves

What are the clinical implications, consequences and therapy for CKD patients?



PABLO UREÑA-TORRES
Paris, France

Among the mitral, pulmonary, tricuspid and aortic cardiac valves, the incidence and prevalence of valvular calcification in CKD have been mainly reported for the mitral and aortic valves. For instance, the annual incidence of aortic valve calcification has been found to be 3.3%. The results of several studies including more than 600 dialysis patients reported a prevalence of mitral valve calcification varying from 25% to 59% (13% prevalence in CKD pre-dialysis patients). For the aortic valve the prevalence is even higher at 28% to 55%. The calcification of both valves occurs 10 to 20 years earlier in CKD patients compared to the general population.

There are several recognized predisposing factors to valvular calcification, including infections, endocarditis, rheumatic heart disease, genetics, systemic diseases such as lupus, Wegener disease, etc., and bone and mineral disorders. An example of a genetic factor is shown in the recent publication of a genomic-wide association study (GWAS) where a single nucleotide polymorphism (SNP) in the lipoprotein A gene was strongly and statistically associated with aortic valve calcification [1].

Cardiovascular disease is the leading cause of mortality in patients with chronic kidney disease (CKD) especially in dialysis patients. More than 50% die from ischemic heart disease, sudden death, arrhythmias, heart failure, strokes or peripheral arteriopathy. It also is generally accepted that calcification of the vascular tree and of the heart valves are closely related to these complications and that they predict the extremely high risk of cardiovascular complications and death in these patients.

Regarding the pathophysiology of heart valve calcification, five major factors can be listed including:

- Mechanicals, since cardiac valves are subjected to an important mechanical stress related to pressure gradients, turbulent blood flow, high peak accelerations and velocities, cycling of opening and closure valves, and high frequency vibration of valve leaflets. This repetitive process can be accelerated in CKD patients because of anemia, arteriovenous fistula volume overload, high cardiac output and hypertension.
- Metabolics, such as hyperlipidemia, oxidized low-density lipoprotein (LDL) cholesterol, diabetes, inflammation and metabolic alteration of end-stage renal disease.
- Ionic factors such as hypercalcemia, hyperphosphatemia, increased Ca x P product, metabolic alkalosis, and hypomagnesemia.
- Hormonal factors, including parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), Klotho, sclerostin.
- Finally, numerous drugs have been related to the development of cardiac valve calcification including calcium salts and calcium-based phosphate binders, vitamin D analogs and vitamin K antagonists.



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April 2016
CHZ/HFER/16/0049

Calcified heart valves can lead either to valvular stenosis with the obstruction of blood flow or to valvular regurgitation because of an inadequate valve closure. The diagnosis of mitral and aortic valve calcification is mainly done by the echocardiogram; however, calcified valves can be often seen in standard X-ray films or scanners. Mitral valve calcification leading to mitral regurgitation is associated to high left-atrium (LA) pressure, pulmonary hypertension, left-ventricular (LV) dilatation and eccentric LV hypertrophy (LVH). The clinical signs are characterized by dyspnea, fatigue, atrial fibrillation, low cardiac output state and pulmonary edema. At the auscultation, a holosystolic blowing murmur at the apex, a S3 gallop and diastolic flow rumble can be heard. When mitral valve calcification leads to mitral stenosis, the normal mitral area of 2-4 cm² can be reduced to < 1 cm², resulting in increased heart rate, shorten diastole cycle, increased pressure gradient between LA and LV, pulmonary hypertension and right ventricle (RV) overload. The typical clinical signs are dyspnea and orthopnea, atrial fibrillation, thromboembolisms and cardiac signs related to RV failure such as fatigue, peripheral edema, hepato-splenomegalia and hoarseness by recurrent laryngeal nerve palsy. The auscultation reveals a low-pitched diastolic rumble at the apex.

As for the mitral valve, aortic valve calcification can lead to valve insufficiency (regurgitation) or stenosis. Aortic valve regurgitation will increase blood pressure at the LV and LA, leading to LVH. There is a large difference between systolic and diastolic blood pressure. Long-term asymptomatic aortic valve regurgitation leads to progressive LV dilatation, dyspnea, frequent and premature LV contractions, and peripheral edema. The auscultation displays a diastolic flow rumble at the apex. When the calcification leads to aortic valve stenosis, the normal aortic valve area can decrease from 2.5-3.0 cm² to the critical surface area of 0.7-0.5 cm². The intra LV pressure is extremely high as well as the LA

pressure. The pressure gradient between the LV and the proximal aorta can attain 50-100 mmHg. Clinically, these patients can have angina, atrial fibrillation, chronic heart failure, pulmonary edema, syncope and sudden death. At the auscultation there is a S4 gallop and a mid-late systolic ejection murmur. Other frequent complications of aortic stenosis are skin and GI bleeds, which are due to a reduction in von Willebrand factor and which are negatively correlated with the mean transvalvular pressure gradient. The Von Willebrand factor is degraded by the ADAMTS13 metalloprotease. These clotting abnormalities are immediately corrected after surgical aortic valve replacement.

Besides these clinical and biological consequences, cardiac valve calcification is also associated with more deleterious general consequences. The presence of either mitral or aortic valve calcification doubled the risk of all-cause mortality in dialysis patients [2]. This risk is higher still when both valves are calcified.

The medical treatment of mitral valve stenosis consists of controlling heart rate with beta-blockers, amiodarone, digitaline, anticoagulation, and statins. Surgery includes valve replacement or endovascular balloon mitral valvuloplasty or commissurotomy. In case of regurgitation, medical treatment includes vasodilators, diuretics, anticoagulation and statins. Valve replacement can be indicated in case of severe disease. In case of aortic valve stenosis and regurgitation medical treatment essentially aims to control blood pressure and heart rate.

The indications for valve replacement in aortic valve stenosis include an aortic area surface < 0.7-0.5 cm², a pressure gradient >50-60 mmHg, an aortic jet velocity >5 m/sec and complications such as infection and bleeding. In valve regurgitation the criteria for valve replacement are the severity of LV dilatation and the regurgitation jet. The classical

form of surgery can be avoided by the use of transcatheter heart valve insertion (TAVI). It should be stressed that CKD and dialysis patients as well as people older than 75 years are no longer contraindicated for valve replacement. However, the per- and postoperative risks of mortality are 15-fold higher in CKD patients.

There is a hope that medical treatment could prevent or attenuate the progression of heart valve calcification in CKD. A randomized clinical trial performed in 186 dialysis patients, who had an electron beam computerized tomography (EBCT) at baseline and after one year of treatment with either a calcium-based phosphate binder or sevelamer, showed that sevelamer therapy stopped the progression of heart valve calcification in 45% of these patients and induced regression in 26%, compared to only 28 and 10% in the calcium group, respectively. Finally, in the ADVANCE study, dialysis patients with secondary hyperparathyroidism, who were treated by cinacalcet for one year, showed a slower progression of aortic and mitral valve calcification score than the control group. ■

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Symposium 21
Calcification and calciphylaxis
Monday, 08.00 – 09.30, HALL D



CARMINE ZOCCALI
Reggio Calabria, Italy

Acute kidney injury: how can we protect the lungs?

Pulmonary complications are very common in AKI patients

Acute kidney injury (AKI) develops in about one out of five hospitalized patients and in about a half of admissions to the intensive care unit (ICU). AKI is the perhaps the most common driver of nephrologists' consultations in hospitals, and notoriously entails a high death risk (33 % in patients requiring dialysis treatment and >50 % in ICU patients). Of concern, patients with full-blown AKI have a longer hospital stay and double the risk of requiring transfer to short-term or long-term care facilities, a risk that is substantially increased in AKI patients who develop acute respiratory failure.

AKI is currently seen as a systemic disease heavily impacting upon the immune system and, via this system, upon virtually all organ functions. The mortality rate remains exceedingly high in this population (≥50 % in ICU patients). Coherent experimental data in animal models and clinical studies in patients with AKI show that this disease has a detrimental effect on the lungs. Pulmonary complications are exceedingly common in AKI patients, and encompass lung edema, respiratory failure demanding mechanical ventilation that is needed for longer when compared to ICU patients without AKI.

Respiratory failure superimposed upon or concomitant to AKI substantially increases the risk of death in this high-risk, acute condition. Lung edema in AKI may have both a cardiogenic origin, being favored by underlying left-ventricular (LV) problems and / or volume overload, or a non-cardiogenic origin, i.e. secondary to extensive endothelial injury attributable to systemic inflammation / immune activation. Early detection and monitoring of lung congestion may be useful for the clinical management of AKI patients.

Cardiogenic pulmonary edema is triggered by volume overload and / or LV dysfunction, which engenders raised capillary hydrostatic pulmonary pressure and transudation of fluid into the interstitium and eventually frank lung edema. Patients can be effectively treated with ultrafiltration or diuretics. Noncardiogenic edema is characterized by lung capillary injury determining protein transudation and substantial increase in lung water, and fluid removal via ultrafiltration or diuresis is ineffective in these patients. The cardiogenic form of pulmonary edema is not associated with inflammatory infiltrates. In contrast, non-cardiogenic pulmonary edema is characterized by bilateral infiltrates on chest X-ray and inflammation. Central venous pressure and pulmonary artery pressure are usually normal or low in non-cardiogenic lung edema.

Chest ultrasound (US) allows detection of pulmonary congestion and may document the severity and the extension of interstitial edema. This technique allows precise count-

ing of the called 'US-B lines', which are an US equivalent of standard Kerley-B lines detected in standard radiograms of the thorax. Importantly, US-B lines reflect water accumulation in the lung interstitium, and the counting of these lines has a high intra- and interobserver reproducibility. Of note, chest US has the potential for the detection of lung congestion at a pre-clinical stage, and preliminary data indicate that it may be useful to assess pulmonary congestion and to monitor the evolution of this alteration in the course of AKI. Thus, clinical decisions about the application and / or the intensification of therapies aimed at countering lung congestion in the course of hospitalization for AKI may be facilitated by systematic application of this technique. A pilot study in a series of AKI patients not requiring mechanical ventilation has clearly documented the superiority of this technique over standard clinical examination (lung auscultation, edema, hemodynamic profiling) for the detection of interstitial lung edema. The results of this pilot study form the basis for a clinical trial testing the usefulness of this technique for guiding lung congestion treatment in patients with AKI. ■

Symposium 23

Cross-talk between kidneys

and other organs in AKI

Monday, 08.00 – 09.30, HALL F

Crosstalk between the heart and the kidney

Why specialists should also speak the same language

For too long, physicians have been trained as single-organ specialists, with cultural barriers impeding a multidisciplinary approach to patients and diseases. The presence of a significant amount of comorbidities in kidney patients, and the fact that nephrologists are probably the last true internists in medicine, are conditions that led to a multidisciplinary evolution of nephrology as a specialty. In particular, today we know that every kidney patient is a cardiac patient as well and this is the reason for increasing interaction between cardiology and nephrology. The nature of heart and kidney interaction is a typical example of a bidirectional organ crosstalk with time windows of hours, days and even months or years. These conditions have allowed the identification of several types of cardiorenal syndrome well summarized by the modern worldwide-accepted definition / classification.

When acute decompensated heart failure or an acute coronary syndrome occurs, several mechanisms are involved in a consequent rapid deterioration of kidney function. Typically we can describe hemodynamic mechanisms summarized in a possible renal hypoperfusion due to arterial underfilling consequent to a low cardiac output state. On the other hand, venous congestion and increased venous pressure in the case of acute diastolic dysfunction may also contribute to a decreased pressure perfusion of the kidney, activating several compensatory mechanisms and neurohormonal derangements. Among them we may see the secretion of vasoconstricting and vasodilating peptides, activation of the renin-angiotensin-aldosterone system, abnormal secretion of arginine-vasopressin, with activation of V2 receptors at the collecting tubular level leading to water and sodium retention and frequent hypervolemia and hyponatremia. In these

conditions, the iatrogenic damage to the kidney may be induced by diuretics but also by other toxic agents including contrast media utilized for imaging procedures. The correct management of fluid balance in these patients is quintessential to avoid edema and congestion, or hypotension and organ hypoperfusion.

Another important mechanism involved in kidney damage during acute heart disorders is inflammation and activation of humoral and cellular pathways, leading to damage to renal tubular cells by necrosis and apoptosis, but also worsening myocardial dysfunction in a vicious circle that amplifies the damage at tissue level. This mechanism has also been demonstrated in case of acute kidney injury as a primary disorder, with a consequent humoral and cellular activation of mechanisms of distant organ damage. Less pronounced, but equally dangerous, is the chronic crosstalk between heart and kidney, leading to progressive scarring and fibrosis and chronic organ dysfunction. While the acute syndromes are more evident and rapidly devastating, the chronic ones are generally subclinical but equally dangerous and leading to bad clinical outcomes.

Another type of cardiorenal syndrome is a secondary form of common heart and kidney damage where the primary disorder is a systemic disease. In the acute setting, this is a condition typically represented by severe sepsis and septic shock. In this condition, humoral and cellular mechanisms are activated with high circulating levels of cytokines and high apoptogenic potential of circulating blood leading to common heart and kidney damage. These humoral and cellular mechanisms reproduce in amplified manner what single-organ damage is causing in acute cardiorenal or renocar-



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diac syndromes. As an example, we can describe the results of some recent experiments where plasma was taken from patients with acute decompensated heart failure. Plasma was incubated with monocytes in vitro and cell apoptosis was studied. The level of monocyte apoptosis at 48 and 72 hours was significantly higher in patients who developed acute kidney injury (AKI) after acute heart decompensation (cardiorenal syndrome type 1) compared to patients who did not develop AKI. The level of circulating cytokines was also significantly higher. Furthermore, we took the supernatant from the experiment and we incubated with it a culture of renal tubular cells. Once again, the level of renal tubular cell apoptosis was significantly higher with the supernatant from patients who developed AKI.

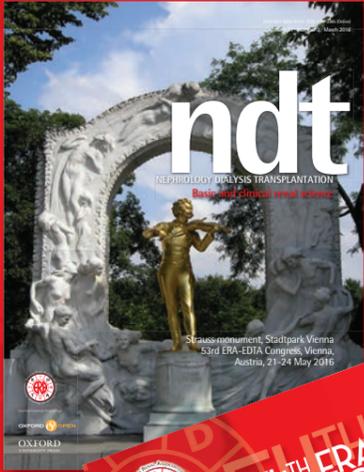
These experiments demonstrate the humoral nature of the heart and kidney crosstalk that cannot be underestimated in the care of these patients. In case of septic patients, only patients with high levels of circulating endotoxin tend to display cardiorenal syndrome type 5. According to these results, a possible rationale for the application of extracorporeal therapies in patients developing cardiorenal syndromes may emerge. Studies will be required to test this hypothesis, and the key factor in such studies will be a close collaboration between nephrologists and cardiologists in a true multidisciplinary strategy. ■



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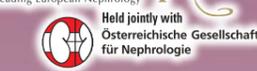
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RUN FOR KIDNEYS

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2016



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

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

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

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

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

Friday, May 20 - 11.00-19.00

Saturday, May 21 - 07.00-19.00

Sunday, May 22 - 07.00-13.00

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

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

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



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Check the 53rd ERA-EDTA Congress official website for further update about the Run for Kidneys 2016!

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In whom, when, and which type of fluid?

CAN INCE

Rotterdam, The Netherlands

SYMPOSIUM 7

Fluid management in the ICU
SUN 11.45-13.15, HALL D



Clinical evaluation of bone disease: what makes sense?

DANIEL CEJKA

Vienna, Austria

SYMPOSIUM 18

Bone, calcium and PTH in CKD
SUN 17.00-18.00, HALL F



Identifying vascular calcification in CKD patients

TERESA ADRAGAO

Cascais, Portugal

SYMPOSIUM 21

Calcification and calciphylaxis
MON 08.00-09.30, HALL D



Pathophysiology of preeclampsia

MATTHEW HALL

Nottingham, United Kingdom

SYMPOSIUM 24

Development and pregnancy
MON 08.00-09.30, HALL B



Is sleep apnea a really major problem in CKD?

SYDNEY TANG

Hong Kong SAR, China

SYMPOSIUM 26

Lingering questions in CKD
MON 11.45-13.15, HALL D



Machine perfusion to preserve or to resuscitate: where are we today?

INA JOCHMANS

Leuven, Belgium

SYMPOSIUM 31

DGF: how to prevent it?
MON 15.15-16.45, HALL E

Tomorrow's Highlights

Plenary Lecture 2

10.45 - 11.30, HALL A

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

SYMPOSIUM 27

11.45 - 13.15, HALL E

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

SYMPOSIUM 30

15.15 - 16.45, HALL D

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

SYMPOSIUM 33

17.00 - 18.30, HALL A

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



CAN INCE
Rotterdam, The Netherlands

In whom, when, and which type of fluid?

State-of-the-art management of the critically ill patient

The condition of shock and sepsis, where—despite correction of systemic oxygen delivery variables—signs of regional dysoxia and a deficit in oxygen extraction persist, represents the true challenge in the hemodynamic management of the perioperative and critically ill patient today. Current evidence shows that the origin of circulatory failure in such patients is not found in alterations in systemic variables, but rather in the microcirculation. Under normal physiology there is hemodynamic coherence between the systemic and microcirculatory hemodynamic, ensuring matching of oxygen supply to the oxygen need of the tissues. However, during critical illness and sepsis, such hemodynamic coherence is lost and microcirculatory alterations can persist despite normalization of systemic hemodynamic variables by therapeutic strategies [1].

These insights have gained clinical acceptance by our introduction of bedside microcirculatory observations using handheld video microscopes (HVM), the most recent generation of which is Cytocam-IDF imaging. This offers greater sensitivity in being able to observe more microvessels than previous generations and incorporating a computer-controlled image sensor [2]. Analysis of these images can directly measure microcirculatory red blood cell (RBC) flow, the promotion of which can be regarded as the ultimate purpose of fluid and vasoactive resuscitation in states of hypovolemia.

Hypovolemia is ultimately defined by microcirculatory and thereby tissue hypoperfusion, and systemic indicators of hypovolemia must be regarded as surrogates of tissue perfusion, the specificity and sensitivity of which can be questioned. From a microcirculatory perspective, therefore, the result of fluid therapy must be to promote an increase in convective flow. Conversely fluid overload results in loss of RBC-filled capillaries, reduced functional capillary density (FCD), increased diffusion distances and loss of oxygen extraction [3].

The final destination of the RBC is to carry its oxygen load to the parenchymal cells and offload its oxygen to the tis-

sue cells to meet their oxygen needs to produce adenosine triphosphate (ATP) via mitochondrial oxidative phosphorylation. Fluids in themselves have little to no oxygen-carrying capacity. Therefore the function of fluids from an oxygen transport perspective is to facilitate and promote the flow of RBC to the microcirculation with the aim of improving oxygen availability to the tissue cells without diluting their oxygen-carrying capacity (for example, capillary hematocrit). However, even though there may be improvement in red blood flow it can come at the cost of diluting the blood and reducing its oxygen-carrying capacity.

Thus fluid therapy is a double-edged sword and administration of fluids should balance between these two opposing results of fluid therapy. Observation of the sublingual microcirculation using HVM is able to distinguish between these two effects and can therefore be used to optimize the volume of fluids administered in states of hypovolemia [2]. In this manner, titration of fluids can be used to identify hypovolemia, which by definition is low convective microvascular flow. Prasnakus and co-workers, in an elegant clinical study in intensive care unit (ICU) patients [4], showed that patients who exhibited clinical surrogates of hypovolemia (for example, oliguria, hyperlactemia, tachycardia) in combination with low microcirculatory flow, but not those with normal microcirculatory flow despite the presence of clinical surrogates of hypovolemia, responded positively to fluid administration in terms of a reduction in the same clinical surrogates of hypovolemia and improved microcirculatory perfusion. Such a distinction could not be made by the fluid responsiveness to stroke volume, which was similar in both groups.

For such an effect to occur, fluids should remain as long as possible in the circulation to promote microcirculatory flow and thus colloids are indicated, as suggested by the CRISTAL trial conducted by Annane and co-workers [5]. Of note is that the majority of colloids used in this study comprised hydroxyethyl starch (HES130/0.4) solutions. However, the CHEST trial, a large randomized controlled trial conducted in ICU patients and comparing 0.9% sodium chloride solutions to starch HES130 / 0.4 solutions, suggested that starch solutions had deleterious effects in comparison to saline when it came to the need for renal replacement, although this study also found that renal injury was more common in the saline group than in the starch group [6]. Nevertheless, the authors concluded that starches are more likely to be asso-

ciated with adverse events and this study was used as one of the bases for the current avoidance of the use of HES solutions. However, there are some shortcomings in this trial, in that these patients were not hypovolemic (normotensive, normal lactates) and in need of colloids, and the methodology of this trial was recently put into question [7].

In conclusion, it seems appropriate from a microcirculatory perspective to use colloid solution only in those patients who are truly hypovolemic and to target microcirculatory flow improvement as an endpoint. If microcirculatory flow is normal or even high, the administration of fluids would not be advisable or should be conducted conservatively despite the presence of clinical surrogates of hypovolemia, the cause of which must be concluded as arising from conditions other than hypovolemia. Crystalloids should be administered in a similar conservative manner. However, if intracellular dehydration is a point of concern, then glucose needs to be included as transmembrane transport of glucose facilitates movement of water to the intracellular compartment [8]. ■

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Vienna, Austria

Clinical evaluation of bone disease: what makes sense?

The answer is that it depends on what you are looking for...

Renal osteodystrophy affects many patients with advanced chronic kidney disease (CKD stages 3 and 4) and virtually every patient with terminal renal failure (CKD stage 5). Because bone has both mechanical and metabolic / endocrine functions, this leads to a series of consequences.

Mechanical stability of bone is impaired in CKD patients. An increased likelihood of bone fracture is well documented with progressive loss of renal function. For instance, the rate of hip fractures, which are often debilitating, is approximately 4 times higher in dialysis patients compared to kidney-healthy matched controls. This increased hip fracture rate leads not only to significant morbidity, but also to increased mortality rates that are approximately doubled after incident hip fractures.

As for all patient groups, increases in fracture risk in CKD patients are not evenly distributed but there probably is some sort of variability within CKD patient cohorts. From a clinical point of view it is therefore of interest to identify the CKD patients who are at highest risk of fracture. For the general population, two tools to estimate fracture risk are well established: measurement of bone mineral density (BMD) by dual X-ray absorptiometry (DXA) and the fracture risk prediction calculator FRAX.

Current KDIGO guidelines on CKD-MBD, which are currently under revision, do not recommend measurement of BMD in patients with CKD stage 3-5D. In the guidelines it is stated that DXA measurements do not predict the type of renal osteodystrophy due to the nature of the test or predict the risk of fracture because of paucity of studies, which were conflicting. This view has changed to some extent as a metaanalysis of available retrospective data suggested that BMD is actually lower in CKD patients with a history of fracture compared to those without [1]. Furthermore, two prospective studies [2,3] reported significantly lower BMD values in CKD patients with incident fractures compared to CKD patients without new fracture.

More sophisticated techniques to study bone structure such as high-resolution peripheral quantitative computed tomography (HR-pQCT, Figure 1) allow for detailed analysis of bone microarchitecture and quantification of structural parameters such as cortical thickness, periosteal perimeter, trabecular number or trabecular separation. However, although HR-pQCT shows some promise in terms of more accurate estimation of bone stability, this technique is still not widely available. Furthermore, HR-pQCT has shown only slightly better results in terms of discrimination of fracture status compared to conventional DXA. This might be due to the fact currently all HR-pQCT-derived parameters (such as cortical thickness for instance) are interpreted separately. Instead, some form of virtual stress testing, which could integrate all the information derived from HR-pQCT measurement to estimate the mechanical stability of measured bone, might increase sensitivity and specificity of this method to discriminate fracture status. However, these methods (for example, finite element analysis [FEA]) are still largely experimental and no ideal in-silico method to estimate fracture risk has been identified yet.

The FRAX calculator (<https://www.shef.ac.uk/FRAX>) was developed by the World Health Organization to estimate the

risk of future fractures. It is validated for many countries using country-specific fracture databases. FRAX provides clinicians and patients with 10-year probabilities of hip and major osteoporotic fractures. Using the results from FRAX (expressed as percentages), patients can understand their fracture risk more easily and can make more informed decisions about whether or not to start bone-specific therapy. The beauty of FRAX is that probability of future fractures can be calculated using patient history and demographics alone. DXA results can be incorporated into the calculation but are not necessarily needed. So far, the FRAX tool has not been validated for patients with CKD. Indeed, results from cross-sectional as well as prospective studies investigating the utility of FRAX in CKD patients do not suggest that FRAX in its current form is useful to identify CKD patients at high risk of fracture [2,4].

From a metabolic perspective, bone serves as a large reservoir of calcium and phosphorus, and is also actively involved in the regulation of phosphorus homeostasis by secretion of fibroblast growth factor 23 (FGF-23) mainly from osteocytes. Bone of healthy adults undergoes constant remodeling, with estimations that the entire skeleton is being replaced approximately once every seven years. This bone remodeling is undertaken by bone-forming osteoblasts and bone-resorbing osteoclasts. In patients with CKD, the activity of bone cells and thus bone turnover can be massively increased as a result of overt hyperparathyroidism, a state that is called high-turnover bone disease or osteitis fibrosa in its most extreme form. On the other side of the spectrum, cellular activity and bone turnover can be decreased, which is called low-turnover bone disease or adynamic bone if no turnover can be detected at all.

Historically, uncontrolled high bone turnover in the presence of uncontrolled hyperparathyroidism was a major concern because of its obvious deleterious effects on bone health with many unprovoked fractures including serial fractures of the vertebrae. Nowadays, with the availability of vitamin D and analogs, cinacalcet or parathyroidectomy, high bone turnover seems less of concern. Instead, the attention has moved to low turnover / adynamic bone disease, which can occur spontaneously under uremic conditions or can result from overtreatment with PTH-lowering substances. Several reports have linked low bone turnover to increased vascular calcification (for example [5]), which is associated with increased mortality in CKD patients. The currently prevailing concept is that adynamic bone, due to the physicochemical properties of bone substance and lack of cellular activity, is unable to buffer short-lived elevations in calcium and phosphorus levels in blood as they occur after meals or during dialysis using high calcium baths.

Given this concept it seems rational to keep bone turnover within 'normal' limits. The problem is that transiliac bone biopsy, which remains the gold standard to determine bone turnover, is invasive and laborious, and obviously not suited for large patient populations. Unfortunately, bone turnover markers such as (bone-specific) alkaline phosphatase, osteocalcin, C-terminal collagen crosslinks and others perform poorly in CKD patients in terms of prediction of bone turnover state. Thus, for the practicing nephrologist the best bet still is to keep PTH levels within target ranges.

The original K/DOQI recommendation to keep PTH-levels at 150-300 pg / ml in dialysis patients was revised in the KDIGO guidelines (PTH target range approximately 150-600 pg / ml), with the aim of avoiding oversuppression of bone turnover and ultimately vascular calcification. This approach has raised quite an amount of debate on whether or not the upper PTH limit of approximately 600pg / ml is too liberal. Data from

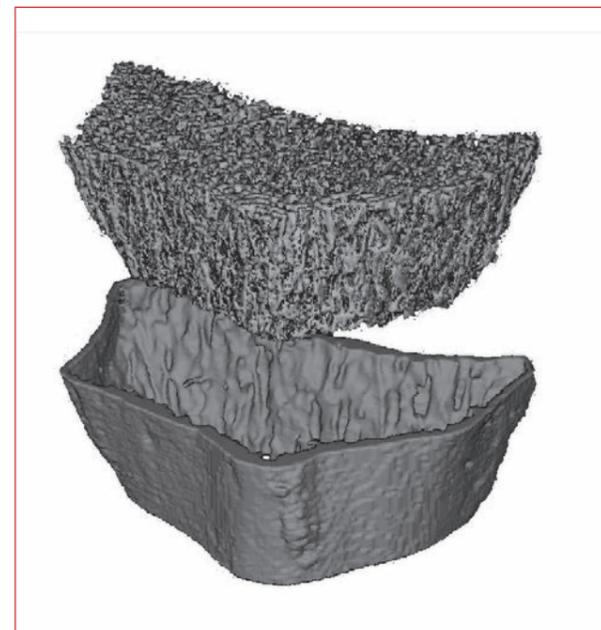


Figure 1: HR-pQCT, 3 dimensional reconstruction of a distal radius of a dialysis patient. Trabecular and cortical regions are shown separately. © Medical University Vienna

one of the largest bone biopsy collections available including 492 dialysis patients from several countries [6] suggest that the lower PTH limit is a reasonable cut-off to work with to discriminate low from non-low turnover and to guide therapy. On the other side of the spectrum, both PTH cut-offs (300 pg / ml and approximately 600 pg / ml) show very high negative predictive values (NPV: 90 % and 86 %, respectively) to differentiate high from non-high turnover. The downside of these cut-offs was that positive predictive values (PPV) were only 34 % for both guideline recommendations. This means that only 34 % of patients with high-turnover bone disease are correctly detected using both PTH cut-off levels, and the majority of patients with high bone turnover are not identified and thus potentially undertreated, irrespective of which PTH cut-off (300 pg / ml or ~600 pg / ml) is being used.

Taken together, if one is interested in mechanical stability and fracture risk, conventional DXA can give an idea about the patient's bone status and fracture risk. If prevention or treatment of high or low bone turnover is the goal, then measuring PTH is the easiest and probably also the most valuable parameter to determine bone turnover. ■

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Identifying vascular calcification in CKD patients

Which are the best methods of evaluation?

Vascular calcification is highly prevalent in chronic kidney disease (CKD) patients and is associated with high cardiovascular risk. Different methods can be used to identify vascular calcification in CKD patients. This information can be used to guide the management of CKD-mineral and bone disorder (CKD-MBD).

Types of vascular calcification

There are 2 types of vascular calcification: intimal and media calcification. Intimal calcification develops during the atherosclerotic process and is a marker of the atherosclerotic burden. Medial calcification does not cause obstruction of the arteries but modifies the properties of the arterial wall, which becomes rigid. Arterial stiffness is diagnosed by the increase of pulse pressure or increase of pulse wave velocity, and contributes to the development of left-ventricular hypertrophy and to decrease in coronary perfusion during diastole. These patients can have coronary insufficiency and angina without coronary stenosis.

Agatston score

Braun J et al. [1] using electron beam computed tomography (EBCT) verified that hemodialysis (HD) patients had a much higher coronary artery calcium score (CACS) evaluated by Agatston score, when compared with non-HD patients with coronary artery disease.

The understanding of the very high Agatston scores in HD patients has been clarified by different studies. Autopsy analysis showed that, when compared with matched non-uremic patients, renal patients had similar calcification in coronary intima but more calcification in coronary media and a more inflammatory response [2]. By comparing in the same HD patients coronary angiography with coronary calcifications evaluated by EBCT, Haydaar AA et al. [3] verified that patients with no occlusive disease on angiography had CACS > 400 and that patients with > 3 diseased vessels on angiography had a CACS > 1000, a value rarely seen in non-CKD patients. These data suggest that total coronary calcification calcium score is the sum of both intimal and medial calcification, and that EBCT or multislice computed tomography (MSCT) cannot differentiate intimal from medial calcification. Raggi P et al. [4] demonstrated that higher coronary artery calcification score was correlated with higher atherosclerosis prevalence.

Prevalence of vascular calcifications in CKD

The prevalence of vascular calcifications is very high in HD patients. In different studies, evaluating CACS with either EBCT or MSCT, the prevalence ranged from 50% to 83%. Using plain X-Ray, in different studies, the prevalence of vascular calcifications ranges from 51% to 81% in HD patients; vascular access calcification was present in 23% of patients. In PD patients, vascular calcification ranges from 41% to 61% of patients; in CKD patients not on dialysis the prevalence ranges from 46% to 73%. The prevalence of valvular calcifications evaluated by echocardiography ranges from 47% to 52% in HD patients and 39% to 47% in PD patients.

The main outcomes that have been associated with vascular calcification in CKD patients are: all-cause and cardiovascular mortality, arterial stiffness and peripheral artery disease (PAD).

Vascular calcifications and mortality

Blacher et al (Hypertension 2001; 38:938-42) demonstrated that vascular calcification, evaluated by ultrasonography in large arteries, predicted mortality in HD patients. Wang et al. [5] showed that valvular calcification evaluated by echocardiography was associated with mortality in PD patients. London et al. [6] verified that intimal and medial calcification evaluated in an abdominal plain X-ray was associated with mortality in HD patients. After these 3 landmark studies, many studies have confirmed the association of vascular calcifications with mortality. Higher Agatston score evaluated by EBCT was associated with mortality in prevalent [7] and incident [8] HD patients.

We have developed a semiquantitative simple vascular calcification score (SVCS) using plain X-ray of the pelvis and hands that ranges from 0 to 8 points [9]. In different studies, a higher SVCS was associated with all-cause and cardiovascular mortality, with peripheral artery disease and with arterial stiffness. Most of these findings using the SVCS have been replicated by other groups. Vascular calcifications evaluated by other plain X-ray methods have been associated with mortality in HD patients: abdominal aortic calcification [10], Kauppila score [11], aortic arch calcification [12, 13] and vascular access calcification [14].

In CKD patients not on dialysis, in opposition to the Kauppila score, the SVCS was also associated with all-cause and cardiovascular mortality [15]. Interestingly, hand calcification was a strong predictor of cardiovascular mortality, drawing attention to the prognosis of medial calcification in the earlier stages of CKD.

Vascular calcification and peripheral artery disease

Data from DOPPS showed that in a cohort of 29,838 HD patients the prevalence of PAD and amputation was, respectively, 24% and 6% [16]. High calcium and phosphate levels were found to be some of the predictors of amputations and the authors hypothesized that vascular calcification could be the link between altered mineral metabolism and PAD. Using the ankle brachial index (ABI) evaluated by Doppler, we verified that calcifications in main arteries (aorta and iliac-femoral arteries) were associated with ABI<0.9 while calcifications in peripheral arteries (pelvic and hands) were associated with ABI>1.3 [17]. This was the first study to demonstrate an association between vascular calcification with ABI in HD patients. As previously demonstrated by Ono K et al. [18], we have also verified that both high and low ABI were associated with all-cause and cardiovascular mortality.

Other non-invasive methods

Other non-invasive methods have been used to detect vascular calcifications in CKD patients. Aortic calcification in lateral dual X-ray absorptiometry (DXA) showed a strong correlation with CACS in the same vessel [19]. Breast calcifications in mammograms were strongly associated with peripheral arterial calcification in hands, wrists, lower legs and feet [20] and can be considered a marker of medial calcification.

Progression of vascular calcifications

Agatston score is the best method to evaluate progression of vascular calcifications and has been used in several clinical trials. Plain X-ray evaluation of vascular calcifications also allows the demonstration that progression of vascular calcification is associated with mortality [21, 13, 22].

In summary

Vascular calcifications are highly prevalent in CKD patients and have a progressive course. The presence and burden

of vascular calcifications are associated with an increased risk of cardiovascular events and mortality.

Computed tomography is the most sensitive method to detect the presence and progression of vascular calcification but, due to the higher cost and the expertise required, is not adequate for use in the daily routine. Plain X-ray is less expensive, uses a lower radiation dose and is adequate for screening. It can also be interpreted by the nephrologist without the need of a radiologist. The identification of vascular calcifications may be used to guide the management of CKD-MBD. ■

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Is sleep apnea a really major problem in CKD?

The evidence indicates an important bidirectional association

The prevalence of obstructive sleep apnea (OSA) is between 3% and 7% in the general population, and has increased dramatically during the last 2 decades along with increased rates of obesity. However, the prevalence of OSA is much greater in patients with CKD.

Sleep apnea (SA) is extremely common in end-stage renal disease (ESRD). Patients on both hemodialysis and peritoneal dialysis have an exaggerated propensity for SA with a prevalence rate of >30% or even higher. Poor sleep quality and sleep disorders have been a recurrent observation in patients with CKD. Sleep disorders such as obstructive sleep apnea (OSA) can contribute to hypertension, diabetes, cardiovascular disease, and worsen obesity, all of which are also independent risk factors for CKD. The lingering question is whether or not the prevalence and severity of SA is already heightened during CKD before its progression to ESRD.

Indeed, several investigators have also observed a tentative relationship between SA and advancing CKD. However, the association is far from established with highly variable SA prevalence rates, ranging from 2.5% to 41%, being reported in this population. Such discrepancies have arisen from inter-study inconsistencies in methodology. While some investigators quoted the apnea-hypopnea index (AHI) to define SA, others have utilized the respiratory disturbance index (RDI). Moreover, the index cut-offs used to represent SA were not uniform across different studies. It is also noted that investigations to date have recruited heterogeneous cohorts for analyses. This is despite epidemiological research demonstrating the prevalence of SA to be a function of age, gender and specific craniofacial anatomy of different ethnicities.

To evaluate the association between the early stages of CKD and SA using the parameters of sleep-disordered breathing (SDB), restless legs syndrome (RLS), and subjective and objective sleep quality (SQ), a cross-sectional analysis of a general population-based cohort was performed in Switzerland, comprising 1,760 adults who underwent complete polysomnography at home. The prevalence of early (stages 1-2) and moderate (stage 3) CKD was 8.2% and 7.8%, respectively, while 37.3% of the entire cohort had moderate-to-severe SDB (AHI ≥ 15 /h) and 15.3% had severe SDB (AHI ≥ 30 /h). SDB prevalence was positively associated with CKD stages and negatively with estimated glomerular filtration rate (eGFR). Patients with early stages of CKD have impaired SQ, and have an increased prevalence of SDB and PLM. After controlling for confounders, objective SQ and PLMI were still independently associated with declining kidney function.

Our group sought to determine the association between SA and CKD by enrolling a highly specific cohort of Chinese male subjects aged 40-60 with different stages of CKD to undergo comprehensive sleep assessments by overnight polysomnography. Of 141 subjects enrolled, the prevalence of SA and nocturnal hypoxemia (NH) was 35.5% and 10.6%, respectively. The adjusted odds ratio (OR) for sleep apnea by body mass index (BMI) and proteinuria were 1.18 (95% confidence interval [CI] 1.02-1.37; $P \leq 0.05$) and 1.57 (95% CI 1.12-2.46; $P \leq 0.05$) respectively. Adjusted OR for median cohort oxygen desaturation index (ODI) by BMI and proteinuria were 1.23 (95% CI 1.05-1.45; $P \leq 0.05$) and 1.75 (95% CI 1.12-2.76; $P \leq 0.05$). These data suggest that SA is prevalent in CKD patients and strongly correlated with BMI and proteinuria.

To further complicate the matter, SA has also been observed to induce CKD. Hence, SA and CKD may have a potential bi-directional relationship. Recent observational studies have shown that SA is associated with increased risk of incident CKD. In a large cohort from Taiwan that comprises 43,434 individuals (8,687 patients with SA and 34,747 matched non-SA subjects), over a mean follow-up of 3.9 years, there were

157 new CKD events in patients with SA and 298 events in the matched non-SA cohort. The respective incidence rates were 4.5 and 2.2 / per 1000 person-years, implying that the risk of CKD development was greater among patients with SA than in the matched non-SA cohort with an adjusted hazard ratio of 1.58 (95% CI 1.29-1.94), which is similar to that for hypertension.

The current literature suggests a bidirectional association between CKD and SA through a variety of potential mechanisms, which predispose to both diseases being possible risk factors for each other. CKD may lead to SA through a repertoire of mechanisms, including alterations in chemoreflex responsiveness, upper-airway (pharyngeal and tongue) edema and narrowing due to fluid overload and redistribution in the recumbent position, and accumulation of uremic toxins. It is conceivable that SA can also accelerate loss of kidney function. Moreover, animals exposed to intermittent hypoxia display histopathological evidence of renal damage. Potential mechanisms of SA-associated CKD include renal hypoxia, hypertension, endothelial dysfunction, activation of the sympathetic nervous system, and increased oxidative stress. Attention to the problem of SA is often underestimated or overlooked in the care of CKD patients. With the aforesaid observations, the answer to the lingering question is that clinical vigilance for SA is of paramount importance when attending to CKD patients with or without significant proteinuria. ■

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Machine perfusion to preserve or to resuscitate: where are we today?

The increased demand for kidneys has led our community to use 'higher-risk' kidney grafts that are donated by sub-optimal donors. These grafts, inter alia from donations after circulatory death or from expanded criteria donors, are more susceptible to preservation injury and have a higher risk of unfavourable outcomes such as delayed graft function and decreased graft survival. It has become clear that static cold storage does not protect kidney grafts from ongoing injury, and organ preservation research is now focusing on dynamic, instead of static, preservation. Dynamic preservation could allow for organ optimization while offering a platform for viability assessment, active organ repair and resuscitation. The concept of dynamic preservation – of which machine perfusion is one modality – is not new. Carrel and Lindbergh first coined the concept in the 1930s. The principle of dynamic preservation is to hook up the kidney to a machine that continuously pumps a preservation or blood-based solution through the organ. Some thirty years later, hypothermic dynamic preservation using plasma or blood-based solutions became a clinical reality. Dynamic preservation was the only way to preserve deceased organs until static cold storage solutions became available. However, because static cold storage offered a simple and

effective way to preserve and transport organs, it soon became the most commonly used storage method. Recently, with increasing use of 'higher-risk' grafts, there has been a resurgence of interest in dynamic preservation strategies. Technological advances have made it possible to not only build reliable and transportable machines, but to also allow dynamic preservation at higher temperatures, bringing us closer to truly sustaining a kidney outside of the body and making it available to viability assessment and resuscitation and repair.

Non-oxygenated hypothermic machine perfusion of the kidney is the oldest dynamic preservation mode. Clinical trials of non-oxygenated hypothermic machine perfusion have shown that hypothermic machine perfusion reduces delayed graft function and may improve graft survival, especially in kidneys from expanded criteria donors. However, there remains some uncertainty as to how long kidneys need to be perfused in order to benefit from hypothermic machine perfusion. We also know that the technique needs further optimisation. Several preclinical studies have shown that cellular metabolism is slower but not at standstill during hypothermic machine perfusion, and that respiration continues to result in oxidative stress. One potential improvement is the addition of oxygen to hypothermic machine perfusion and this is currently being investigated in clinical trials. Assessing viability of the kidney during hypothermic machine perfusion has been disappointing so far, and the options for resuscitation and repair are likely to be limited.

Machine perfusion at more physiological temperatures is therefore being explored. A short period of normothermic machine perfusion at 37°C immediately before implantation has been found to improve kidney graft function, replenish ATP and reduce injury in a number of large animal models, and the technique is now being investigated in clinics. In contrast to hypothermic machine perfusion, kidney function can be evaluated during normothermic machine perfusion by assessing the macroscopic appearance of blood perfusion, renal blood flow and urine output, but proof of concept for transplanting kidneys that were discarded and subsequently resuscitated by normothermic machine perfusion has not yet been reported. Subnormothermic machine perfusion – at room temperature – is also being explored. This technique is more physiological than hypothermic machine perfusion, and because the cellular metabolic need at these temperatures is lower than in normothermic conditions, it may be possible to use acellular perfusion rather than blood-based solutions.

Lastly, tools for assessing graft quality, predictive of transplant outcome, need to be developed and validated to aid decision-making on whether to utilise or discard kidneys.

Over the past decade, the focus of attention for the transplant community has shifted towards improving preservation in order to make the best use of a scarce resource. Machine perfusion has the potential to change the way that organs are preserved and has become the subject of a growing body of research. ■

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Pathophysiology of preeclampsia



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A pregnancy-related syndrome of seizures, oedema and poor fetal growth was identified by Hippocrates and Plato over 2000 years ago. In the 17th century, the abrupt onset of the condition and its associated visual symptoms led Varandeuus to call the syndrome eclampsia, from the Greek *εκλαμψια* meaning "light burst". Very little progress in understanding the condition was made until the 18th and 19th centuries when it was recognised that seizures were preceded by the development of proteinuria, elevated blood pressure and oedema – a condition that came to be known as preeclampsia.

Further observations through the 20th century identified the placenta to be at the root of preeclampsia development. Symptoms and signs resolve following delivery and placentae from pregnancies affected by preeclampsia were noted to contain areas of infarction. Histological specimens from earlier in affected pregnancies revealed a defect in the normal maturation of the maternal-fetal-placental unit. In normal pregnancies, placental trophoblasts invade maternal spiral arteries to create large, low resistance vessels capable of providing adequate blood flow for normal fetal development. In pregnancies destined to be affected by preeclampsia, a failure of adequate trophoblast invasion – for whatever reason – results in placental under-perfusion, ischaemia and impaired fetal growth.

How does placental ischaemia lead to the maternal syndrome of hypertension, proteinuria, liver dysfunction, coagulopathy, seizures and renal dysfunction? We have moved on from Hippocrates' theory of the "Wandering Uterus" in which he proposed that during pregnancy, the uterus moved freely through the body in search of satisfaction, capable of wreaking havoc upon the liver, lungs and head. Multiple competing theories were reported over decades, complicated by variation in definition of the condition, a lack of robust animal models to test proposals and a plethora of observed epiphenomena that lacked pathophysiological correlation.

A significant breakthrough occurred early in the 21st century. Colleagues from the National Institute of Child Health and Human Development, Bethesda and Harvard Medical School identified an altered balance of placenta-derived angiogenic and anti-angiogenic growth factors during pregnancies af-

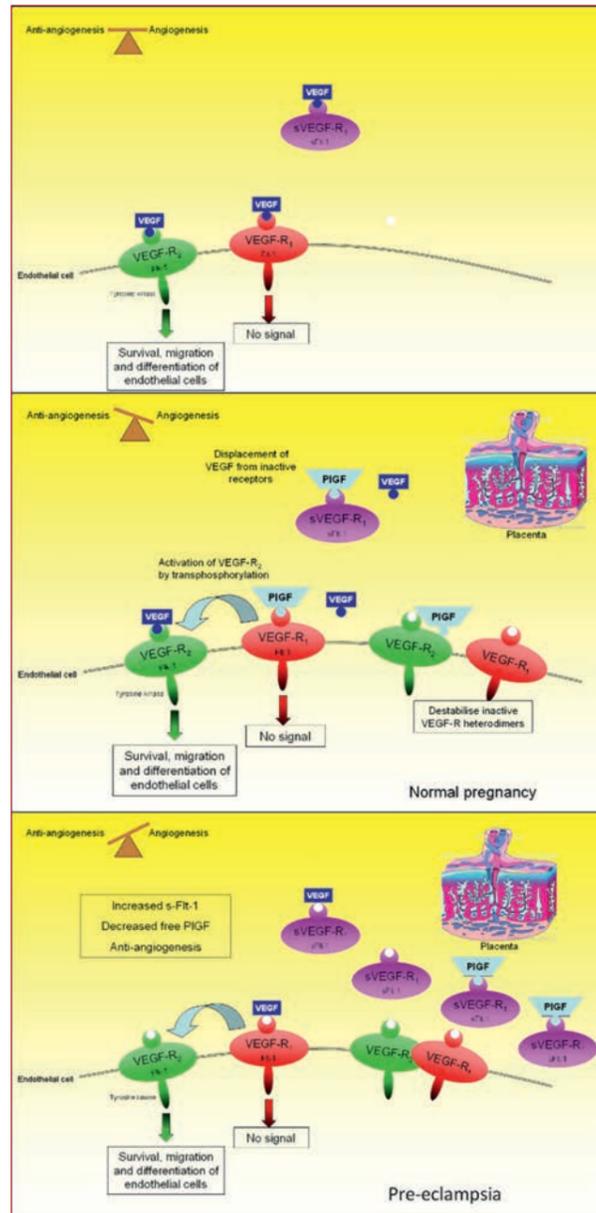


Figure 1 © Hall

ected by preeclampsia. In normal pregnancy, angiogenesis is promoted by release of Placental Growth Factor (PIGF) that acts to displace VEGF from inactive receptors and up-regulate active receptors. Soluble fms-like tyrosine kinase-1 (s-Flt-1) is a circulating decoy receptor for VEGF that limits this upregulation to maintain an appropriate balance. Preeclamptic pregnancies were shown to be associated with increased s-Flt-1 and decreased PIGF in the maternal circulation – a plausible mechanism for the widespread endothelial dysfunction and clinical syndrome.

Despite preeclampsia affecting between 2 and 8% of pregnancies worldwide – approximately 250,000 affected births per year in Europe alone – awareness of the syndrome for over 2 millennia, and an increasing understanding of the pathophysiology, predicting which women are most likely to develop the condition during pregnancy remains difficult. There has also been negligible progress in preventing preeclampsia occurring or halting the disease once established. These are the challenges ahead. ■

Networking in Nephrology is essential

National Societies' Meeting

On Thursday afternoon the ERA-EDTA invited representatives of the national societies of nephrology to a joint meeting. The aim was to forge alliances, learn from each other and, thus, to strengthen European Nephrology. More than 50 delegates from more than 40 countries attended the meeting and took the opportunity for vivid discussions. A hot issue, for example, was the question of how to handle the problem of refugees with ESRD. Due to the current refugee crisis in Europe about 1-1.2% of the dialysis population has refugee status with often unclear reimbursement situation. As Professor Wim van Biesen, Belgium, pointed out, this is something that needs to be regulated, because the decision, whether a refugee can be dialyzed, cannot be made on an individual level. "We nephrologists believe we have the moral duty to take care of these patients and provide them with the treatments they need - and therefore we have to put pressure on authorities to find solutions quickly". Political pressure is also important when it comes to the question of CKD prevention. The European Kidney Health Alliance (EKHA), of which the ERA-EDTA as well as some of the national societies are members, raises awareness of CKD among EU politicians. Chairman of the EKHA, Professor Raymond Vanholder, presented the 'EKHA Recommendations' and appealed to the national representatives to circulate them to their national health politicians and, thus, to initiate CKD prevention strategies on national levels. Another important point that was discussed was the implementation of a European Nephrology Exam, which can be taken from next year onwards in addition to national exams and will facilitate access to jobs in other European countries. Among other initiatives that were present-



Presidents of the national societies and ERA-EDTA Council Members

ed at the meeting was the certification of renal units by the German Society of Nephrology as well as the launch of the European Nephrology Portal. ■

Poster Sessions

Do not miss the presentation of innovative results during the poster sessions today and tomorrow (09:30-10:45 in the Poster Area located in the Exhibition Hall). Interested viewers have the opportunity to meet and speak informally with the authors, which facilitates the exchange of ideas and opens up networking opportunities. Poster presentations are often the first chance for young investigators to present their work at big congresses, so come along, support the young colleagues and, thus, find out about tomorrow's science and today's brand new study results!

To be presented today: The NICOREN Study

The NICOREN study is a multicenter, open-label, randomized study that was published in NDT and will be presented as one of the Late Breaking Clinical Trials Posters at the congress in today's poster session (09:30-10:45 in the Poster Area located in the Exhibition Hall). Aurelie Lenglet and colleagues examined the non-inferiority and safety of nicotinamide (NAM) when compared with sevelamer (SEV) in chronic hemodialysis patients. One hundred patients were randomized to either NAM or SEV treatment for 24 weeks. It showed that both drugs are equally effective in lowering serum phosphorus, but patients' tolerance of NAM was largely inferior to that of SEV. ■

(continued from page 1) President of the Austrian Society (ÖGN), gave his welcome address to this joint congress of the ERA-EDTA and the ÖGN. Another special highlight was the announcement of collaboration among ASN, ERA-EDTA and ISN by the presidents of these societies. Then in a video message Karen Kadenbach, Member of European Parliament, commented on health policy making from the perspective of the European Community, before Professor Raymond Vanholder delivered an inspirational speech on costs of kidney diseases and the stony path to a healthier society. ■

What's on in Vienna today?



Klimt, Kupka, Picasso and others

Form Art
Unteres Belvedere / Orangerie
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Stars of David. The Sound of the 20th Century

Jüdisches Museum Wien / Museum Dorotheergasse
Sunday - Friday, 10.00 - 18.00



Wiener Staatsoper live outdoors

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

Sunday, 22 May, 18.00
DON CARLO, Giuseppe Verdi

Dear Delegate,

We hope that you are enjoying this year's ERA-EDTA Congress. Did you know that the Association publishes two journals?



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

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ERA-EDTA
Press Office

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



Impressions from Day 1

