Renal replacement therapy in Turkey

Both the prevalence and the incidence of end-stage renal disease (ESRD) requiring renal replacement therapy (RRT) have been rising over the past years in Turkey. “We see chronic kidney disease as a rapidly growing major public health problem in our country,” says Professor Cengiz Utas, Head of the Nephrology Department of Emsey Hospital in Istanbul, Turkey. The rising figures, however, have been paralleled by improvements in the field of nephrology and RRT. The number of dialysis centres, for example, increased from 333 in 2000 to 1009 in 2011.

For a closer look to the details of this development, Professor Utas refers to the statistics of the Turkish Registry of Nephrology, Dialysis, and Transplantation which is coordinated by the Turkish Society of Nephrology. Among prevalent patients in 2011, the most common RRT modality was haemodialysis (HD, 82.3% of patients), followed by peritoneal dialysis (7.7%) and kidney transplantation (9.9%). The point prevalence of end-stage renal disease requiring RRT (including paediatric patients) was found to be as high as 809 pmp, while incidence rates amounted to 236 pmp in Turkey. There are two main reasons underlying the low penetration of peritoneal dialysis: the first is low reimbursement for peritoneal dialysis and the second is privatisation – in private centres, only haemodialysis is reimbursed. The age of HD and transplant patients is increasing, with a predominance of male patients (see also figures 1 and 2).

The most common diseases leading to RRT were diabetes mellitus, hypertension, and chronic glomerulonephritis. “Actually, cardiovascular disease is the leading cause of mortality in dialysis patients,” says Professor Utas and continues by saying that “healthcare spending for RRT amounts to 1.15 billion euros per year in Turkey, corresponding to 5% of the total healthcare budget.” Direct costs of dialysis in Turkey are summarised...
The **LBT session on Sunday dealt with promising treatment options and potential markers to predict outcomes.**

Late-breaking news in renal care

The **ISSUE 3**

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Patients with chronic kidney disease frequently suffer from anaemia. Therefore, current therapy to increase levels of haemoglobin often involves administration of erythropoisis-stimulating agents (ESA) as well as iron substitution. The PRIME study of Ajay Gupta of Rockwell Medical, Wixom, U.S.A., was designed to examine the efficacy of soluble ferric pyrophosphate (SFP) on the doses of ESAs needed to treat anaemia in patients on haemodialysis. SFP is a unique iron preparation which can be delivered to the patient via dialysate. Results demonstrate that SFP administered over a period of nine months can significantly reduce the end-of-treatment need for ESA by 35%, compared to conventional dialysis, while maintaining haemoglobin levels. Moreover, no SFP related adverse events were observed and the drug does not lead to iron overload. By reducing ESA doses, SFP may thus enhance patient safety in terms of stroke and malignancies and may also lower costs.

Antibacterial honey is active against a broad range of fungi and bacteria and has proven effectiveness in preventing haemodialysis catheter infections. However, in a randomised controlled open-label study presented Wednesday, daily topical exit-site application of antibacterial honey didn’t prove to be superior to current standard care for the prevention of catheter-related infection in peritoneal dialysis (PD). In her trial, Carolyn van Eps of the Princess Alexandra Hospital in Brisbane, Australia, enrolled 371 PD patients with a median age of 65 years to daily topical exit-site application of antibacterial honey plus standard exit site care (n=186), or to nasal mupirocin prophylaxis plus standard exit site care (control, n=185). Rates of exit site infection in the antibacterial honey and control groups were 0.37 and 0.29 episodes per patient year, respectively (incident rate ratio [IRR] 1.25, 95% CI: 0.88, 1.79, P=0.22). Diabetic PD patients receiving antibacterial honey experienced significantly higher risks of both the primary composite outcome and peritonitis. “Honey cannot be routinely recommended for prevention of ESIs in PD patients,” van Eps concluded.

Sevelamer carbonate (SevCarb) treatment can restore function of the estrogen receptor gene ERs in both women and men with diabetic kidney disease (DKD), according to a study presented by Gary Striker, Mount Sinai School of Medicine, New York. This effect was coupled with reduced oxidative stress and inflammation, improved anti-oxidant defences, a decrease in cardiovascular risk and lower levels of markers indicating DKD progression. In the trial, subjects were randomised to SevCarb (n=50, 4800mg/day) or CaCO3 (n=56, 1590mg/day) for six months and analysed for levels of ERα (p=0.003) and two markers indicating defence reactions against anti-oxidants and advanced glycation end products (Nrf2, p=0.009 and AGER1, p=0.028).

To date, no significant benefits of pharmacological cholesterol lowering have been demonstrated for patients on haemodialysis. Thus, it remains to be established which of them should receive cholesterol lowering and when to start this therapy. Study data presented by Guenther Silbernagel from Bern, Switzerland indicate that assessing cholesterol absorption may help to identify those who might benefit from statins. The team studied 1,255 participants of the 4D study who were on chronic HD and suffered from diabetes. Patients received either 20 mg of atorvastatin (n=619) or placebo (n=636). Cholesterol absorption was estimated from the ratio of circulating cholesterol to cholesterol (CR). In the atorvastatin group, the tertiles of CR were predictive of cardiovascular risk and all-cause death. (3rd vs. 1st tertile: HR=1.75, 95% CI: 1.25–2.46; p=0.001 and HR=1.48, 95% CI: 1.07–2.03; p=0.017, respectively), but not in the placebo group (3rd vs. 1st tertile: HR=1.02, 95% CI: 0.74–1.40; p=0.914 and HR=1.01, 95% CI: 0.75–1.36; p=0.929, respectively).

High concentrations of high-density lipoprotein (HDL) cholesterol are considered to indicate efficient reverse cholesterol transport which may protect against atherosclerosis. However, HDL may be dysfunctional in end-stage renal disease (ESRD). In their study, Winfried Maerz from Mannheim, Germany, and his colleagues conducted a post-hoc analysis of the ‘Deutsche Diabetes Dialyse’ (4D) study to investigate the impact of HDL cholesterol and its major protein components, namely apolipoproteins A1, A2, and C3 on the outcomes of diabetic HD patients. In their analysis, high concentrations of apolipoprotein A2 were associated with decreased risk of the composite vascular endpoint (4th vs. 1st quartile: HR=0.74, 95% CI: 0.58–0.96) and all-cause mortality (4th vs. 1st quartile: HR=0.63, 95% CI: 0.49–0.80). However, a consistent relation between high-density lipoprotein cholesterol, apolipoprotein A1 and C3 quartiles and end points could not be found. Maerz concluded: “HDL metabolism may be of relevance for type 3 patients on haemodialysis, but this is poorly reflected by measuring HDL cholesterol. Moreover, in CKD the function of HDL-C may change below glerular filtration rates of 60 mg/ml and high cholesterol may offset the effect of LDL lowering by statins.”

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**Table 1: Direct costs of haemodialysis per patient (HD, Euro/year).**

<table>
<thead>
<tr>
<th>Service</th>
<th>Outpatient clinic</th>
<th>Tests</th>
<th>Hospitalisation</th>
<th>Reimbursement of HD</th>
<th>Cost of drugs</th>
<th>Total costs</th>
</tr>
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<tr>
<td></td>
<td>245</td>
<td>19</td>
<td>46</td>
<td>9.625</td>
<td>1.510</td>
<td>11.445</td>
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</table>

**Table 2: Direct costs of peritoneal dialysis per patient (PD, Euro/year).**

<table>
<thead>
<tr>
<th>Service</th>
<th>Outpatient clinic</th>
<th>Tests</th>
<th>Hospitalisation</th>
<th>Cost of drugs</th>
<th>Cost of PD solutions</th>
<th>Total costs</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>253</td>
<td>507</td>
<td>209</td>
<td>820</td>
<td>6.912</td>
<td>8.701</td>
</tr>
</tbody>
</table>

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**Legend:**

<table>
<thead>
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<th>Image</th>
<th>Description</th>
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FRESENIUS MEDICAL CARE

The impact of nutrition on kidney disease

Diets and enteral supplements can significantly improve outcome of patients with CKD.

Nutritional abnormalities, especially decreased nutrient intake has been known as a hallmark of advanced kidney disease for a long time. The retention of uraemic toxins leads to a number of nutritional and metabolic derangements that affect the quality of life and overall survival of these patients. Professor Alp Ikizler became interested in the nutritional aspects of kidney disease about 20 years ago because: “I was intrigued by the possibility to make an impact on the overall well-being of these patients by improving their nutritional and metabolic profiles.”

He is coming home to Istanbul, where he was born and trained, to present at the third plenary lecture of the congress on how and why nutritional interventions could lead to a better outcome of patients with chronic kidney disease (CKD).

Protein-energy wasting is associated with heightened risks of morbidity and mortality in patients with kidney disease. Ikizler specifies three major factors contributing to abnormal nutrient balance and subsequence protein-energy wasting (PEW) in chronic kidney disease: first, inappropriate dietary nutrient intake relative to the ongoing needs; second, hormonal and metabolic derangements related to kidney disease; and third, adverse nutritional effects of renal replacement therapy in patients on maintenance dialysis therapy. With regard to optimal diets, he emphasises: “It is very important to clearly differentiate between CKD patients on dialysis and those not on dialysis as they exhibit two different metabolic and nutritional profiles. One of the key issues is the adjustment of the nutritional therapy for those patients with disease progression.” For patients with earlier stages of kidney disease, he assumes that physicians more often have to deal with obesity and its associated risk factors than with protein-energy wasting. Ikizler also explains why exercise is useful for CKD patients. He states that the maintenance dialysis therapy and worsening uraemic milieu.

Appropriate diets for dialysis patients

As much as it is a life-saving modality, the haemodialysis procedure increases the metabolic rate and leads to an energy catabolic process, much like running a marathon. In addition it is a protein catabolic process due to losses of about 30 grams of protein equivalent of amino acids into the dialysate. Furthermore, the exposure of blood to non-self material (the dialysis tubes, membrane and dialysate) activates inflammatory pathways, which further exacerbates the overall catabolic milieu. Ikizler concludes: “Under these circumstances, there is almost a doubling of protein and calorie needs compared to healthy individuals.” He strongly recommends patients eating during dialysis, hence to compensate for their needs at the time they are excessively catabolic. He even suggests to overfeed them a little to create an anabolic response – to build some protein mass. When dialysis is initiated, there is a clear-cut change in the patient risk profile and for nutritional requirements, which is primarily driven by the maintenance dialysis therapy and worsening uraemic milieu.

Plenary Lecture: 3:

Improving outcome of patients with CKD: diets and enteral supplements

Alp Ikizler, Vanderbilt University School of Medicine, Nashville, USA, currently performs studies that are aimed at defining tools to assess nutritional and metabolic derangements and to examining the aetiology of these abnormalities with a specific emphasis on renal replacement therapy and insulin resistance. Another research focus is on testing strategies to prevent or treat PEW and to exploring the link between PEW and clinical outcomes such as hospitalisations or death and health care costs.

From: 9:45 to 10:30
Practical challenges in managing Thrombotic Microangiopathies (TMAs)

Chairman: Professor Oguz Soylemezoglu
Ankara, Turkey

Monday, May 20th 2013, Emirgan Room /ICC-B2

12:45 - 12:50 Introduction
Professor Oguz Soylemezoglu
Ankara, Turkey

12:50 - 13:15 Considerations in diagnosing TMAs
Professor Franz Schaefer
Heidelberg, Germany

13:15 - 13:40 Treatment of aHUS in native and non-native kidney
Professor Neil Sheerin
Newcastle, United Kingdom

13:40 - 13:45 Closing remarks
Professor Oguz Soylemezoglu
Ankara, Turkey
The Young Nephrologists' Platform

Young colleagues are encouraged to join ERA-EDTA’s new YNP group.

Last year, the ERA-EDTA decided to create a new body – the Young Nephrologists’ Platform (YPN) represents the interests of young doctors within the ERA-EDTA. Although the YNP Board was just confirmed by the ERA-EDTA Council in the end of February 2013, YNP is already quite popular among young ERA-EDTA members: 104 nephrologists at the age of 40 years or younger have joined the new group since last year. Most of them come from Italy; however, countries such as Belgium, France, Germany, Poland, Romania, Sweden, Turkey and UK are also prominently represented.

This positive feedback reflects the current need of young nephrologists for professional support. “Many of us are familiar with new technologies, computers and the internet and most importantly, we are open for cooperation. However, young colleagues often work in regional or small hospitals without having access to high-level consultation or continuing medical education at universities,” YNP chair Miklos Zsolt Molnar elaborates. The goals of YNP are guided by these needs and thus the new group is strongly committed to improve educational opportunities, to promote research activities, involve young nephrologists in all ERA-EDTA activities, and improve collaborations among young clinicians and scientists in Europe. Members already came up with a number of suggestions, according to Miklos Molnar: “We may consider for example the creation of databases covering clinical questions to provide online support; moreover, it might be a good idea to participate in shaping nephrology diplomas or tests that will harmonise education all over Europe. In addition, one could think about providing free ERA-EDTA memberships for young nephrologists based on their research results, and organising special CME courses and short joined congresses focusing on one research topic.” Before implementing proposals, however, it is important to know what the ERA-EDTA is expecting from their young members. Molnar explains: “We sent an online questionnaire to all ERA-EDTA members, asking them about their expectations regarding the output of our group, their preferred communication channel to boost the dialogue with young members and the topics they would be interested in.” The results of this survey will be presented during the YNP session at the ERA-EDTA Congress in Istanbul. Molnar is looking forward to extending the YNP scientific network in Istanbul and would like to encourage young colleagues to join the new group. There is a lot to gain.

The YNP Board

Seven young scientists introduce themselves.

Miklos Zsolt Molnar

The Chair of YNP Board, born in 1977, is an associate professor of medicine at the Institute of Pathophysiology, Semmelweis University in Budapest, Hungary. Currently, Molnar is working in Toronto. Dr. Molnar has authored or coauthored over 100 research papers including in high-impact peer reviewed journals and serves as a reviewer for more than 15 journals, for example the Journal of the American Medical Association, Kidney International, the American Journal of Kidney Disease, Nephrology, Dialysis and Transplantation, and the Clinical Journal of the American Society of Nephrology. His main research interests focus on epidemiology and outcomes, anaemia, inflammation, nutrition and sleep disorders in kidney transplant recipients.

Maria Majernikova

Dr. Makernikova was born in 1975 in the Slovak Republic. She completed her specialist training in internal medicine in 2008. In September 2008 she became a PhD student at the University of Groningen, Netherlands. Between September 2008 and October 2009 she joined the University of PJ Safarik in Kosice as a researcher and she pursued academic work at the Department of Public Health Medical Faculty between November 2009 and June 2011. In 2011, she took her board exam in nephrology. Her PhD research focused on investigating the medical (included graft loss and mortality) and psychological determinants of self-rated health in kidney transplant recipients. At present, Dr. Majernikova is working at the Nephrology and Dialysis Centre Fresenius Medical Care – Dialysis Services Slovakia in Kosice as a nephrologist. Her main clinical interests include anaemia, inflammation, nutrition, acute kidney injury, vascular access and dialysis modalities.

Mariusz Kusztal

Dr. Kusztal was born in Poland in 1976. He graduated in medicine from the Wroclaw Medical University in 2001 and completed a four-year course at the Postgraduate School of Molecular Medicine in Warsaw in 2006. In 2006, he successfully defended his PhD thesis in the field of kidney transplantation. He received his board certification in Internal Medicine (2008) and in Nephrology (2011). Currently, he holds the position of an assistant professor at the Department of Nephrology and Transplantation Medicine, Wroclaw Medical University. He presented and published numerous papers in the field of dialysis, vascular access and transplantation, having received several awards, for example from the ERA-EDTA for his abstracts presented at the congresses in 2005, 2007 and 2010, and from the Polish Society of Transplantation in 2008 and 2011.
Since 2011, he has been supporting NDT-educational.org as a consultant for dialysis.

**Ana Carina Ferreira**

Dr. Ferreira was born in 1979 in Lisbon, Portugal. She graduated in medicine from the New University of Lisbon in 2003. Between 2004 and 2005, she did her general internship and started a specific training in nephrology at the Hospital Curry Cabral, Lisbon, afterwards. In 2012, she obtained the degree of a special-ist in nephrology, ranking number one on a national level. Currently, she works as an attending physician in the Department of Nephrology at Hospital Curry Cabral; moreover, she serves as a clinical coordinator of the Haemodialysis Centre Dialverca and is an invited assistant at the Faculty of Medical Sciences of the New University of Lisbon. In 2013 she was invited to join the editorial board of the Portuguese Journal of Nephrology and Hypertension (PJNH). She presented and published numerous papers in the field of clinical nephrology and transplantation; in 2008, 2009, 2010 and 2011 she received several national scientific awards for presentations of scientific abstracts during annual congresses and for publishing articles in PJNH. She was co-author of the ERA-EDTA Young Investigator Award 2008.

**Davide Bolignano**

Dr. Bolignano was born in 1980 in Reggio Calabria, Italy. He graduated in medicine from the University of Messina (Italy) in 2004 and obtained post-graduate specialisation in nephrology in 2009, both cum laude. He currently works as a clinical researcher of the Italian National Research Council (CNR) at the Institute of Biomedicine and Molecular Immunology (IBIM) based in Reggio Calabria. In 2008, he obtained the “Best Young Researcher Award” by the University of Messina for his outstanding scientific performance; he also received awards from the ERA-EDTA (in 2008, 2010 and 2011) and the Italian Society of Nephrology (in 2010) for scientific abstracts presented during annual congresses. His main research interests include epidemiology and pathophysiology of chronic and acute kidney diseases, renal biomarkers, cardiovascular risk, vasopressin system, medullar and systemic effects of erythropoietin and stem cells in uraemia.

**Giovana Seno Di Marco**

Dr. Di Marco was born in Brazil in 1976, where she obtained her degree in biomedical sciences and her PhD in basic renal science in 2004. After a postdoctoral fellowship in Paris (2005), she moved to Germany (2006), where she is active at the University of Medical Sciences of the New University of Lisbon. In 2013 she was invited to join the editorial board of the Portuguese Journal of Nephrology and Hypertension (PJNH). She presented and published numerous papers in the field of clinical nephrology and transplantation; in 2008, 2009, 2010 and 2011 she received several national scientific awards for presentations of scientific abstracts during annual congresses and for publishing articles in PJNH. She was co-author of the ERA-EDTA Young Investigator Award 2008.

Afterwards, he obtained a post-graduate nephrology fellowship at Necmettin Erbakan University. As a nephrology fellow at the University of Colorado School of Medicine, he also explored aspects of apoptosis and autophagy in a mouse model of cold ischaemia and the role of IL-33 in acute kidney injury. During annual congresses in 2010 and 2012, Kültigin Turkmen has been awarded by national and international societies. His main interests include pathogenesis of inflammation, malnutrition and vascular calcification in chronic kidney disease, renal transplant, autosomal dominant polycystic kidney disease and the quality of life in haemodialysis and peritoneal dialysis.

**Kültigin Türkmen and Charles Edelstein in the lab.**

The organizing committee is very pleased to announce the third ERA-EDTA Renal Run, which will take place on Monday, May 20, 2013 at 15:45. This year runners will enjoy a 2.7 km run through the historical Yıldız Park (Beşiktaş), one of the most beautiful landscapes in Istanbul.

The area of Yıldız used to be a forest in Byzantine times. Sultans during the reign of Suleiman the Magnificent, the sultans made it their hunting grounds. In the next centuries, it remained as a grove behind the seaside palaces. Currently, Yıldız Park is a beautiful garden complex set on a very large park of flowers, plants and trees, gathered from every part of the world dating from the Ottoman era. Park grounds offer panoramic views of the Bosphorus. Runners will definitely enjoy the environment during this time of the year.

The participation in the race is intended for Congress participants. They will be divided into categories according to age and gender. Registration is free, but still must be done for administrative purposes. Online registration will be also possible at the ‘Renal Run Info Desk’ that will be situated in ICEC main entrance.

Registration to the Renal Run can be done up to Sunday, May 19, 2013 at 15:00. Each participant will receive a number and a t-shirt. Refreshments will be provided in Yıldız Park, and cloakrooms will be available in the ICEC.

We are looking forward to your participation and wish you a very enjoyable and fun experience.
Contrast-induced nephropathy

Recently, the European Renal Best Practice working group issued a position statement on the CIN KDIGO guidelines.

AKI is a serious condition that affects kidney structure and function acutely, but also in the long term. Even mild, reversible AKI conveys the risk of persistent tissue damage, and severe AKI can be accompanied by an irreversible decline of kidney function and progression to end-stage kidney failure.

Recently, the European Renal Best Practice (ERBP) working group issued a position statement on the KDIGO guidelines, in order to deal with the lack of supporting evidence for many sections, leading to regional variations in practice. The author’s presentation in Istanbul will deal with the diagnosis and prevention of contrast-induced nephropathy (CIN) and is summarised as follows:

- For the sake of clarity and uniformity, the definition and grading of CIN should be the same as for AKI: ↑SCR, 26.5–44 μmol/l (AKI stage 1). This is slightly different from ESUR criteria (↑SCR by >25% or 44 μmol/l in the three days following intravascular administration of contrast).

- On the other hand, the importance of urinary output for diagnosing contrast-induced nephropathy should be emphasised. In high-risk patients, a repeat serum creatinine should be performed 12 and 72 h after administration of contrast media.

- Before an intervention which encompasses a risk for CIN, baseline serum creatinine should be determined. The risk/benefit ratio of administering contrast should be balanced, and alternative imaging methods should be considered. CIN risk becomes clinically significant at baseline eGFR < 45 ml/min/1.73 m². The risk of CIN also increases in the presence of diabetes and dehydration, it may be lower when simple intravenous contrast is administered for imaging compared to contrast administration during an invasive intra-arterial procedure. The risk increases with the volume of contrast applied. Concurrent nephrotoxic medication would have to be stopped for days or even weeks before contrast administration. Contrast administration should be delayed until dehydration from diuretics use or other clinical circumstances has been corrected.

- Pharmacological prevention strategies of CIN are based on volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, either by oral or intravenous route. In patients receiving appropriate fluid and salt loading, N-acetyl cysteine (NAC) could confer a supplementary protection against CIN, but this should never replace adequate fluid loading. Theophylline, fenoldopam, prophylactic haemodialysis of haemofiltration are not recommended.

References


The work-up of a living donor

If elderly donors are considered, one should be aware of the reduction of kidney function with age.

Over the last decades living donation has become a very important additional source of kidney transplants. Although the risk for the donor seems to be limited, there are some concerns, as the act of donation is a surgical procedure in an otherwise healthy person. Thus, special emphasis has to be put on the donor’s safety.

Current guidelines are dealing with donor protection in different ways. One could argue by analogy, that if no data are available which suggest a certain criterion to be a risk factor for the donor, this risk factor is simply no additional risk. By contrast, one can also argue by analogy that without any data on a certain risk factor the risk is too great to consider a person with this condition a potential living donor.

In fact, there are only very limited long-term data on living donors, none of which indicate a substantial risk for a healthy donor.

What is an acceptable additional risk for a living donor? To some extent this is an individual decision, which may also depend on the relation between donor and recipient. For a reasonable foreseeable future, the donor should not depend on dialysis himself or die due to donation. The ERBP team has put a lot of work into the writing of guidelines for the acceptance of living donors, considering both the safety of the donor and the interest of the recipient.

Based on these guidelines a thorough work-up of the potential donor is indicated. There is no upper age limit to donation in general. If elderly donors are taken into consideration, one should be aware of the reduction of kidney function with age. This could be a problem for the donor itself and for recipient. Thus, elderly people should donate to similarly aged recipients.

Contraindications to donation include diabetes mellitus, most forms of kidney diseases, overt proteinuria and severe hypertension. The question remains how we define these conditions in the case of a potential living donor? Regarding blood pressure, values of less than 140/90 mmHg without antihypertensive medication on at least three occasions are defined as normotensive. In patients on antihypertensive medication or with a blood pressure above 140/90 mmHg, ambulatory 24h blood pressure measurement should be taken. In hypertensive subjects with target organ damage, living donation should be discouraged. For proteinuria, this definition is much more stringent.

Uwe Heemann, Technical University of Munich, Germany

S41: Pre-emptive and living kidney transplantation: the way to improve patient outcomes?

ESOT-DESCARTES Joint Symposium

Room: Rumeli A

Date: 21-05-2013

From: 8:00 to 9:30
Vaccination against the renin-angiotensin system has been an attractive approach to treatment of hypertension and prevention of cardiovascular disease because of evidence for the pathogenic role of angiotensin II in these processes and the therapeutic benefits of angiotensin-converting enzyme (ACE) inhibitor, angiotensin type 1 (AT1) receptor blocker (ARB) and renin inhibitor therapies.

One particular attraction of this approach is the possibility of improved patient compliance with one immunisation every few months rather than the need for daily oral therapy. However, a vaccination strategy presents a number of concerns. These include the wide variation between patients in their antibody response (both titre and affinity) and their renin response to vaccination, the delayed reversibility of renin-angiotensin system blockade by vaccination, particularly during episodes of hypovolaemia, the exacerbation of postural hypotension, the difficulty of monitoring the extent of renin-angiotensin system blockade and titrating renin-angiotensin system blockade by vaccination.

There are also a number of theoretical and practical obstacles to vaccination against the renin-angiotensin system. The assumption that angiotensin II is the culprit in hypertension and cardiovascular disease may be incorrect, particularly in states where renin and angiotensin II levels are not elevated, and ACE inhibitor, ARB and renin inhibitor therapies may produce therapeutic benefits by mechanisms independent of inhibition of the action of angiotensin II on the AT1 receptor. Initial attempts at renin vaccination were almost universally successful as a strategy for reduction of blood pressure in renin-dependent animal models of hypertension and in the spontaneously hypertensive rat, a model that does not have elevated renin and angiotensin levels. However, one consequence of renin immunisation was autoimmune disease of the kidney, characterised by anti-renin antibody deposition in the juxtaglomerular apparatus and progressive interstitial inflammatory injury of the kidney. Moreover, there are theoretical arguments that angiotensin immunisation may have limited effectiveness and clinical studies confirmed these limitations. Angiotensin immunisation may also produce anti-idiotype antibodies directed against the AT1 receptor that may cause disease.

Vaccination against the AT1 receptor is another possible approach but has yet to undergo clinical evaluation. There are, however, serious concerns about possible adverse effects of such a strategy. Autoantibodies against the AT1 receptor have been implicated in many pathological processes including focal segmental glomerulosclerosis, renal allograft rejection, hypertension and preeclampsia.

In summary, the therapeutic benefits of vaccination against the renin-angiotensin system remain to be established and there are many reasons for concern that this strategy may produce harm.

Duncan J. Campbell, University of Melbourne, Melbourne, Australia

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Reprogramming the kidney to self-repair

Microvesicles act as effectors of stem or progenitor cell action.

Several studies suggest a paracrine/endoctrine action of stem/progenitor cells. In fact, the beneficial effect observed in different experimental models of acute and chronic kidney injury after treatment with endothelial progenitor cells (EPCs) or multipotent mesenchymal stromal cells (MSCs) is associated only with minimal engraftment and differentiation of these cells into renal parenchymal cells. Therefore, the concept of stem cell plasticity has been revised and the beneficial effect has been attributed to factors produced by stem/progenitor cells.

Among these factors exosomes/microvesicles (MVs) released into extracellular space emerged as effectors of stem/progenitor cell action. After receptor-ligand interaction, MVs can be incorporated by parenchymal cells transferring several bioactive molecules from the cell of origin, such as receptors, growth factors, bioactive lipids and nucleic acids. By acting as signalling complexes, MVs may directly activate the parenchymal cell. In addition, MVs can transfer transcripts and transcriptional regulators from the cell of origin to the recipient cells, thereby inducing epigenetic and functional changes. Stem/progenitor cell-derived MVs may reprogram neighbouring cells leading to acquire stem cell-like properties. MVs released from EPCs and MSCs contain defined patterns of miRNA typical for the cell of origin. Once transferred to recipient cells, miRNA is translated into proteins. In fact, in vitro and in vivo studies using reporter mRNAs demonstrated their translation into proteins, suggesting that the mRNA delivered by MVs is functional.

As a consequence of mRNA horizontal transfer, EPC-derived MVs are able to activate pro-angiogenic programme in quiescent endothelial cells by triggering transcription of critical constituents of pro-angiogenic pathways. With a similar mechanism, MSC-derived MVs activate regenerative programmes and limit cell injury in renal tubular epithelial cells. Moreover, MVs contain and may deliver microRNA (miRNA), post-transcriptional modulators of gene expression that may induce functional and phenotypical changes in the recipient cells. For instance, MVs released from EPCs may deliver miR-126 and miR-296 leading to activation of angiogenesis.

Dicer silencing to generate miRNA-depleted EVs, or selective inhibition of angio-miRNAs demonstrated that the angiogenic and renoprotective effects of MVs released by EPCs in renal acute ischemia reperfusion injury are mainly dependent on their miRNA content. From the site of injury, MSC-derived MVs were shown to induce dedifferentiation of tubular epithelial cells and cell cycle re-entry by transfer of miRNA that regulate proliferative pathways. Moreover, MVs may transfer MSC-specific functional RNAs capable of altering gene expression in recipient cells which induces up-regulation of BCL-XL, BCL2 and BIRC8 anti-apoptotic genes, and down-regulation of genes involved in cell apoptosis such as CASP1, CASP6 and LTA. Therefore, after incorporation of stem/progenitor cell-derived MVs, resident renal cells are reprogrammed to self-repair parenchymal injury. Indeed, when administered in vivo in different experimental models of acute renal injury, MVs mimic the effect of the stem/progenitor cell of origin and accelerate the functional and morphological recovery of the kidney.

References:

When lymphocytes damage the kidney

AL amyloidosis is quite common among lymphoproliferative diseases with renal consequences.

Kidney damage in lymphoproliferative diseases (LPD) is variable and includes specific lymphoid infiltration with acute kidney injury as well as different kinds of organised and non-organised paraprotein deposition with tubular and glomerular involvement, for example in cast nephropathy, acquired Fanconi’s syndrome, amyloidosis, immunotactoid and cryoglobulinaemic glomerulonephritis (GN), monoclonal immunoglobulin deposition disease, proliferative GN with monoclonal deposits of IgG and IgA, specific GN with IgM deposition, paraneoplastic GN, treatment complications and other miscellaneous types with variety of clinical presentations. All of them may accompany clinically overt LPD or can be their first presentation, a major challenge to the nephrologist.

In our study we aimed to evaluate the incidence of different LPD, predominantly presenting with kidney involvement, and define morphological variants of kidney lesions in LPD patients, who were admitted to the nephrology unit due to nephrotic syndrome, urine sediment abnormalities and/or impaired kidney function.

Using an electronic database we searched 222 patients with LPD treated in our unit between 1994 and 2012, including multiple myeloma (MM), ‘primary’ amyloidosis (PA), Waldenström’s macroglobulinaemia (WM), non-Hodgkin’s lymphoma/leukaemia (NHL/CLL), Franklin disease (FD), Hodgkin’s lymphoma (HL), Castleman disease (CD), monoclonal immunoglobulin deposition disease (MIDD), and monoclonal gammopathy of undetermined significance (MGUS). In addition to routine procedures, work-up included also serum and urine immunochemistry.
Two critical decisions in treating elevated serum phosphorus:

WHEN & HOW

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Product Summary: Renvela 800 mg film-coated tablets. Renvela 2.4 g powder for oral suspension. Active substance: sevelamer carbonate. Subject to medical prescription. Composition: Each tablet contains 800 mg sevelamer carbonate. Each tablet also contains microcrystalline cellulose, sodium chloride and zinc stearate. The tablet coating contains hypromellose and diacetylated monoglycerides. The printing ink contains iron oxide black (E172), propylene glycol, isopropyl alcohol and hypromellose. Each sachet contains 2.4 g sevelamer carbonate. The powder contains propylene glycol alginate, citrus cream flavour, sodium chloride, sucrose, ferric oxide (E172). Therapeutic indications: Renvela is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis. Renvela is indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus > 1.78 mmol/l. Renvela should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease. Contraindications: Hypersensitivity to the active substance or to any of the excipients. Hypophosphataemia. Bowel obstruction. Possible side effects: The safety of sevelamer (as either carbonate and hydrochloride salts) has been investigated in numerous clinical trials involving a total of 969 haemodialysis patients with treatment duration of 4 to 50 weeks (724 patients treated with sevelamer hydrochloride and 245 with sevelamer carbonate), 97 peritoneal dialysis patients with treatment duration of 12 weeks (all treated with sevelamer hydrochloride) and 128 patients with CKD not on dialysis with treatment duration of 8 to 12 weeks (79 patients treatment with sevelamer hydrochloride and 49 with sevelamer carbonate). The most frequently occurring (> 5% of patients) undesirable effects possibly or probably related to sevelamer were all in the gastrointestinal disorders system organ class. Most of these adverse reactions were mild to moderate in intensity. Data possibly or probably related to sevelamer from these studies are listed by frequency here next. Gastrointestinal disorders: nausea, vomiting, upper abdominal pain, constipation (very common) and diarrhoea, dyspepsia, flatulence, abdominal pain (common). The reporting rate is classified as very common (>1/10), common (≥1/10, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), including isolated. Post-marketing experience: During post-approval use cases of pruritus, rash, intestinal obstruction, ileus/subileus and intestinal perforation have been observed in patients during treatment with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate.

Dietary fat manipulation can improve outcomes in chronic kidney disease.

Eating healthily not only provides protein and calories, it also provides many other nutrients that are generally deficient in patients with chronic kidney disease (CKD) and that play important roles in immune function, oxidative stress regulation, and anaemia etc. Dietary fat, for example, typically represents 30% or more of total daily energy intake.

At a general population level, replacement of dietary saturated fatty acid (SFA) with polysaturated fatty acid (PUFA) has been recommended for the prevention of cardiovascular diseases. However, healthy dietary fat may exert additional beneficial effects of particular interest in the context of renal diseases. Available evidence suggests poor quality of dietary fat in the CKD population, with insufficient PUFA and excess SFA intake. Less is known about the implications of this poor dietary fat quality in individuals with CKD. In his lecture, Juan Jesús Carrero-Roig will discuss the potential benefits of dietary fat modification in CKD patients, including plausible effects on disease progression, albuminuria, lipoproteins, inflammation, thrombosis, and clinical outcomes.

The implications of excess SFA intake are poorly investigated, but may link to systemic inflammation and poor outcomes. The most studied dietary fat in terms of supplementation studies regards the n-3 PUFA from fish origin, due to its effectiveness in reducing inflammation and cardiovascular risk in general and in disease-specific populations at risk. Increasing evidence supports the concept that n-3 PUFA may be used as a therapeutic option in reducing proteinuria, as well as serum triglycerides and inflammation in dialysis patients. However, published studies are usually of short duration and underpowered. Excitingly, research published in the last months demonstrates possible benefit of n-3 PUFA supplementation on graft patency and disease progression. In addition, emerging evidence suggests that linoleic acid, the essential n-6 PUFA from vegetable oils, may also be beneficial for a number of CVD risk factors.

Dietary fat goes beyond omega 3 fatty acids, and despite ensuring good nutritional status we have the possibility to tackle specific risk factors through dietary fat manipulations. The optimal dietary fat quality will be discussed and hypothesised, but probably does not deviate from that of the general population: increased consumption of oily fish as part of plant-based diets with low content of SFA. Such dietary fat replacement is likely to benefit patients who have CKD, or are at risk of developing CKD. These recommendations would be, after all, in line with the ‘mediterranean diet’ concept and are also in line with current dietary guidelines for cardiovascular disease prevention.

Juan Jesús Carrero-Roig, Karolinska Institute, Stockholm, Sweden.

S37: Inflammation, oxidative stress and cardiovascular risk in CKD
Room: Uskudar
Date: 21-05-2013
From: 8:00 to 9:30
51st ERA-EDTA Congress
Amsterdam
The Netherlands
May 31st - June 3rd 2014
www.era-edta2014.org
Kidney diseases in China and Europe

In a joint symposium on Monday, the Chinese Society of Nephrology and the ERA-EDTA will discuss renal care topics.

The ERA-EDTA congress is delighted to announce a joint symposium with the Chinese Society of Nephrology, which offers a platform to discuss the epidemiological and clinical challenges of renal care in China and Europe. Here, Professor Zhi-Hong Liu, President of the Chinese Society of Nephrology (CSN) and scientists of the ERA-EDTA Registry in Amsterdam provide an outlook for the data they are going to present today.

IgA nephropathy – the most common kidney disease in China

IgA nephropathy accounts for 45% of primary glomerular diseases in China, according to CSN President Professor Zhi-Hong Liu, 36% of patients will progress to end-stage renal disease (ESRD) within 20 years. Unfavorable renal outcome is indicated by five independent predictors in patients with IgAN, including proteinuria, hypertension, impaired renal function, hypertriglyceridemia and hyperuricaemia. “Sustained proteinuria during the follow-up (time-average proteinuria, TA-P) was the strongest predictor of renal failure,” Zhi-Hong Liu explains. “Compared with TA-P <0.5 g/d, patients with TA-P 0.5-1.0 g/d were associated with a 9.1-fold increased risk of a worse outcome (ESRD or 50 % reduction in eGFR), and patients with TA-P >1.0 g/d were associated with a 46.5-fold increased risk (P < 0.001).” Zhi-Hong Liu and her team at the Jinling Hospital of Nanjing University School of Medicine performed a validation study of the Oxford classification in a multicentre cohort of 1026 patients with IgAN from China. Tubular atrophy/interstitial fibrosis (T) was found to be the most powerful lesion for predicting IgAN independent of clinical features, while mesangial hypercellularity (M) and segmental glomerulosclerosis (S) had only weak influence on renal survival. Repeated renal biopsy revealed that endocapillary hypercellularity (E), crescents (C) and glomerular necrosis (N) were reversible in most of patients with IgAN after treatment. Persistence and emergence of crescents or glomerular necrosis at repeat biopsy indicate an unfavourable renal outcome during the follow-up.

Based on these findings, a multicentre randomised controlled clinical trial was conducted to see the effect of immunosuppressive therapy on proliferative IgAN (patients with E, C or N lesions). 140 biopsy-proven IgAN patients were recruited in this study, mycophenolate mofetil (MMF) treatment was applied at 1.5 g/d for six months, using prednisone (0.6 mg/kg/d) as a control. Remission was observed in 84% of the patients in the prednisone group; moreover, newly formed crescents (C) and glomerulus necrosis (E, C or N lesions) were reversible in most of the patients in the MMF group and 78% in the prednisone group. During immunosuppression, the incidence rates of Cushing’s syndrome (56% vs. 2%) was also significantly higher in the prednisone group; moreover, newly diagnosed diabetes mellitus (17% vs. 2%) was also significantly higher in the prednisone group. These data indicate that IgAN patients with proliferative lesions benefit from immunosuppressive therapy based on renal histology. Mycophenolate mofetil treatment has fewer side effects compared to prednisone.

The burden of chronic kidney disease in Europe

The wide variation in definitions for prevalence and progression of chronic kidney disease (CKD) complicates attempts to compare the burden of chronic kidney disease between European countries. Moreover, standardised definitions for a useful comparison are lacking, according to Dr. Katharina Brueck, Dr. Vianda, Dr. Rosanna Coppo, Turin, Italy...
Late-breaking clinical trials part II

Today's LBT session sets the focus on drugs in chronic kidney disease.

Don’t miss the second late-breaking trial session of this ERA-EDTA congress covering the following topics:

Atrasentan in diabetic kidney disease

Prof. Dick de Zeeuw, Groningen, The Netherlands: Optimal control of albuminuria is the goal of therapy in CKD patients who are not yet on dialysis. In this study, the authors evaluated, whether atrasentan, a selective endothelin receptor A antagonist, could further reduce albuminuria in type 2 diabetes on top of maximum tolerated labelled doses of inhibitors of the renin-angiotensin system inhibitors (RASi).

The COSMOS study

Prof. Jorge Cannata-Andia, Oviedo, Spain: The effect of PTH-lowering drugs (PTH-LG) on survival is a controversial issue. The ‘Current Management Of Secondary Hyperparathyroidism – a Multicentre Observational Study’ (COSMOS) evaluates the association between the use of PTH-lowering drugs and survival.

Safety and efficacy of a novel iron-based phosphate binder

Prof. Juergen Floege, Aachen, Germany: Hyperphosphataemia requires phosphate binders to control serum phosphate (sP). The trial presented is a phase 3, long-term open-label study which was set up to investigate the safety and efficacy of PA21, a novel polynuclear iron(III)-oxyhydroxide phosphate binder, vs sevelamer carbonate in dialysis patients with hyperphosphataemia.

Effect of cinacalcet on all-cause mortality

Prof. Juergen Floege, Aachen, Germany: Although randomised controlled trials (RCTs) are the gold standard for assessing pharmaceutical interventions, their generalisability may be limited by restrictive entry criteria or by their experimental nature. Observational research (OR), on the other hand, may complement RCT findings, but is prone to bias. Propensity score-matched (PSM) studies can reduce bias with regard to measured confounders. In his presentation, Juergen Floege will show data from a PSM trial designed to study the effect of cinacalcet on all-cause mortality (ACM), and compare them to ACM data from the EVOLVE randomised controlled trial.

The OPERA study

Dr. Angela Wang, Hong Kong, Special Administrative Region of China: Vitamin D has been suggested to play a role in cardiovascular disease through interaction with the vitamin D receptor. The OPERA study examined the effect of oral paricalcitol on left ventricular mass and function in patients with chronic kidney disease.

$S 33$: Late-breaking clinical trial session
Room: Rumeli B
Date: 20-05-2013
From: 16:15 to 17:45

Seeking a road map for optimal renal care

Renal care models in Canada may inspire European health systems, too.

Aproximately 1.7% of Europe’s total healthcare budget is spent on patients with end-stage renal disease (ESRD) – a disproportionate expenditure in relation to the much smaller percentage of the population affected. In view of this huge economic burden, the ERA-EDTA invited several well-known health care experts from Europe and outside to Istanbul to join a pan-European healthcare session and discuss the specific situation in their home countries. The keynote presentation of this session was given by Canadian nephrologist Adeera Levin, who reported about the experience with comorbid renal patients in her home province British Columbia.

Renal care in Canada is publicly funded, irrespective of a patient’s age or employment status, while the structures for renal care delivery are based on defined provincial planning models. Public funding in British Columbia, as in several other Canadian provinces, covers clinical programmes and integrated information management systems for all the different aspects of renal care. Basically, five geographic healthcare authorities take care of organising larger and smaller care units, which interact in a kind of mother-sibling relationship to ensure coordinated care.

Kidney disease is a complex condition which often coexists with other conditions, such as diabetes and cardiovascular disease. “When developing a model of care, we should integrate this complexity, a patient-centered philosophy and the healthcare environment in which we are living,” Levin stated in her presentation and continued by saying that “the philosophy of a care model should be consistent with the way the disease goes: longitudinal, multidisciplinary, evidence-based and collaborative both within and between specialties and primary care.” Levin cited a number of studies showing that a multidisciplinary approach may indeed pay off. “We for example did a randomised observational cohort study in both Italy and Canada, where we looked at patients followed for quite a long time before starting on dialysis.” Patients were treated by a nephrophilist alone and compared with a scenario where the nephrophilist collaborated with a multidisciplinary team. Not only were the laboratory parameters better in those treated by the team approach; even more importantly, if those starting on dialysis were seen by the team, they actually lived longer compared to those treated by the nephrophilist alone.

Levin also collected data to justify an integrated care clinic and found that duplicate testing led to costs of at least 5 million dollars a year due to multiple specialists visits. In another trial, she randomised 150 patients to retain their multiple specialty clinics or come to a combined clinic for three years.

“Interestingly, we had less doctors’ visits in the combined group and we were able to improve symptom control for those patients,” she summarised the results. Moreover, such an approach to renal care in patients with complex renal disease would result in potential annual cost savings of 250 million dollar per year in British Columbia, according to a conservative calculation. Levin concluded that successful chronic disease management does not only require understanding of complex disease processes, the right protocols, and the correct identification of key populations, but also a coordinated team approach and a continuum of care funding.
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