Active vitamin D did not prevent cardiovascular disease in dialysis patients included in the prospective, randomized Japan Dialysis Active Vitamin D (J-DAVID) trial. Indeed, on intention-to-treat analysis the cardiovascular risk of treated patients was even slightly increased, although it was not significant (p = 0.127). J-DAVID included 976 patients, who were randomized to treatment with oral VDRA or treatment without VDRAs.

VDRAs are known to raise serum calcium and FGF23 levels, which are both associated with higher cardiovascular risk. “Thus, these effects might have outweighed potential beneficial effects of the supplementation of active vitamin D,” commented Tetsuo Shoji (Osaka, Japan). Outcomes of other randomized controlled trials (e.g., PRIMO or OPERA) that investigated the role of VDRAs in predialysis patients with elevated PTH have also been disappointing. “Based on our results there is no rationale for a VDRA therapy in dialysis patients with normal PTH.”

Franz Schaef er (Heidelberg, Germany) reported that a single course of rituximab is significantly more effective than 12 months tacrolimus in maintaining disease remission in children with steroid-dependent nephrotic syndrome (SDNS), according to a study from India. After 12 months, 90% of children receiving rituximab were relapse free compared with 63% of the tacrolimus group (p < 0.001). Children treated with rituximab also needed significantly lower steroid doses, and had better growth, and better kidney function. Franz Schaef er concluded that, given its excellent tolerability, rituximab may be considered as first-line steroid-sparing therapy in children with SDNS. The open-label, single-center, parallel-arm trial randomized 120 children with SDNS either to 12 months tacrolimus plus tapering doses of alternate day prednisolone or to a single course of rituximab. Tacrolimus was dosed at 0.2 mg/kg/day targeting 5–7 ng/ml trough level, while rituximab was given as two to four weekly infusions at 375 mg/m² depending on circulating B-cell count.
Late breaking clinical trials

The COSMOS study (Current management of sec-
ondary hyperparathyroidism: A multicentre ob-
servational study) showed that reducing serum phosphate by 1.1 mg/dL, from mean serum phos-
phate values of 6.5 mg/dL, towards 3.8–5.2 mg/dL (COSMOS serum phosphate safest target ranges) was associated with 12% reduction in the rel-
ative risk of mortality in hemodialysis patients. The lowest risk of mortality was seen in patients achieving the COSMOS target ranges.

COSMOS was a three-year, open cohort, prospec-
tive, observational study conducted in 6,797 he-
modialysis patients randomly selected from 257 centers in 20 European countries. José Luis Fernández Martín (Oviedo, Spain) of COSMOS said: “For the first time, using a COSMOS analy-
sis that mimics as much as possible what hap-
pens in randomized clinical trials, it was found that the reduction of serum phosphorus in dial-
ysis patients may render the expected benefits, as it is associated with better survival.”

A home-based, low-intensity exercise program significantly improves physical performance in hemodialysis patients, according to the random-
ized, controlled EXCITE (EXerCise Introduction To Enhance performance in dialysis) clinical trial presented by Giovanni Luigi Tripepi (Reggio Cal-
abria, Italy). The 296 patients included in EXCITE were randomly assigned either to the active arm (exercise, n = 145) or the control arm (n = 151). After six months, patients in the active group had a remarkable improvement in their performance either for the Six Minute Walking Test or the Sit-
to-stand-to-sit Test, while no changes were re-
corded in the control group. Changes in cognitive function and in quality of social interaction items of the KDQOL-SF were also significantly more fa-
vorable in the exercise group.

In post-trial follow-up of six months, the risk of hospitalization was significantly reduced in the exercise arm compared to the control arm. The risk reduction (~29%) for hospitalization was confirmed when the same analysis was extended to the post-trial observation period of 36 months. The lowest risk of hospitalization was seen in the subgroup with high adherence compared to the control arm and to patients with low adherence. These results indicate that a simple, person-
ized, home-based, low-intensity exercise pro-
gram managed by dialysis staff improves phys-
ical performance and quality of life, and reduc-
es short- and long-term risk of hospitalization in patients who maintain a high adherence.

In the AURA-LV trial, treatment with low-dose voclosporin for 48 weeks trebled the chance of complete remission of lupus nephritis compared to placebo in patients receiving recommended standard immunosuppressive therapy (OR: 3.21, p < 0.001; high dose 2.10, p = 0.026). Voclospo-
rin was well tolerated with no adverse effects on renal function, blood pressure or serum electro-
lytes. According to lead investigator James Tumlin (Chattanooga, United States): “This study demon-
strates that Voclosporin has positive additive ef-
fec ts on Lupus nephritis concurrent with a rapid reduction of oral steroids. These promising data are a basis for a phase 3 study to validate the ef-
ficacy of low-dose voclosporin in lupus nephritis.”

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The Council will intensify its efforts to root the ERA-EDTA more deeply within the professional and scientific life

Interview with Professor Carmine Zoccali, new president of the ERA-EDTA

You have been elected as ERA-EDTA President. What, in your eyes, are the most urgent tasks the association has to deal with?

The ERA-EDTA is half a century old and an association which is firmly established in all the European countries and in countries bordering Europe. The association is a healthy and successful enterprise. European nephrologists form a cohesive community and, at variance with political Europe, our renal association has no urgent task to face. The association should multiply its efforts in promoting research and education in nephrology in Europe and worldwide, and at strengthening its links with patients, patients’ associations and society at large.

I value teamwork and joint endeavors most of all. Over the past two decades, the ERA-EDTA has grown considerably and in this phase of its history it needs consolidation and reorganization. I have a series of proposals for in-depth discussion within the Council. These proposals revolve around the structuring of the ERA-EDTA into two main areas, Clinical Governance and Outcomes Research, and Laboratory Research, including five branches, various committees and advisory boards. The challenge is to enable these boards and committees to collaborate efficiently and to produce proposals and solutions that can be integrated into the work of nephrologists.

There is a coherent thread in the way the association has developed, and the ideas currently on the table represent the maturation of old and new issues that have been discussed at various levels within the ERA-EDTA over the years. The Council will intensify its efforts to root the ERA-EDTA more deeply within the professional and scientific life of its enormous membership. In my vision, the boards and the committees should voice the perceptions and the needs of the renal community as captured by esteemed colleagues with clinical, scientific and human experience. Strengthening the links with national associations is certainly a priority. I believe that we can better serve the renal community, if the complexities of the profession in Europe are analyzed and monitored by its best clinicians and investigators and by the nephrology leadership at country level.

So I see the committees and boards as an open and transparent powerhouse that will help the association to pursue successfully its mission of fighting kidney diseases by sustaining the advancement of renal sciences. In two words, consolidation and integration are today’s priority for the ERA EDTA.

What are the aims of ERA-EDTA in the long-run?

The triad composed of basic and clinical research, promoting disease prevention, and education is and will remain the mantra of our association for the years ahead.

Where do you see the main challenges for nephrology in Europe in the coming years? And what is your agenda for answering these challenges?

There is no question that CKD is a public health priority. The epidemiology of renal diseases has changed profoundly over the years, but nephrological research has not been sufficiently focused to take account of the epidemiological changes. The current epidemic is mainly driven by hypertension and obesity/diabetes, but scientific research into these conditions is still less in other areas forming the traditional “hunting grounds” of nephrology, such as research on glomerulonephritis and immune-mediated renal diseases, which are relatively rare causes of ESRD in most countries. The ERA-EDTA should have an advisory group to support and advocate public health policies aimed at fighting the CKD epidemic, also by supporting the allocation of research resources according to epidemiologic priorities. A consulting committee will be formed to serve that purpose. One goal of this committee will be to help the European Kidney Health Alliance (EKHA) in advocating public support for CKD research in critical areas in nephrology.

Are there any changes and innovations ERA-EDTA members can expect during your presidency?

Maybe new projects you would like to initiate? One of the most exciting and successful initiatives of our association is the launch of Working Groups in 2009, an idea conceived by Prof. Gerhard London during his presidency. Most ERA-EDTA Working Groups are very successful and have a robust flow of scientific products that serve to advance renal science as well as renal care. Integration and collaboration is an inescapable paradigm in the modern scientific world. The Council will boost its efforts to stimulate collaboration among ERA EDTA working groups. New initiatives to foster collaboration between working groups will be considered by the Council in the near future, including special incentives to engage in such collaboration, and managerial support for the submission of collaborative, multi-group projects to the European commission and other potential funding bodies.

‘Carpediem’ available in English now

Three years ago, Professor Claudio Ronco, Vicenza, Italy, revealed his innovative ‘CARPEDIEM’ dialysis machine for babies to the medical world. At the ERA-EDTA Congress, he presented a case history that was published at the same time in ‘Carpediem’.

The cardiovascular system is a target tissue for vitamin D, and a poor vitamin D status, which is present in the majority of chronic kidney disease (CKD) patients, is a risk factor for cardiovascular mortality. 25D or 1,25D levels begin to decline in CKD patients in early Stage 2. 1,25D falls more steeply and in an earlier phase of CKD — therefore, VDR activation deficiency is an early feature of CKD that might not be reversed by giving exclusively 25D.

1,25D is a novel negative endocrine regulator of the renin-angiotensin system

By late Stage 3 disease, when phosphate is elevated and calcium is low, there is an increase in the incidence or prevalence of hyperparathyroidism. By Stage 5, the majority of patients have hyperparathyroidism. Inappropriate activation of the renin-angiotensin system, which plays a central role in the regulation of blood pressure, electrolyte and volume homeostasis, may represent a major risk factor for hypertension, heart attack, and stroke.

Evidence from clinical studies has demonstrated an inverse relationship between circulating vitamin D levels and blood pressure and/or plasma renin activity, but the mechanism is not understood. Renin expression and plasma angiotensin II production increase several fold in VDR-null mice, leading to hypertension, cardiac hypertrophy, and increased water intake. However, the salt- and volume-sensing mechanisms that control renin synthesis are still intact in the mutant mice.

In wild-type mice, inhibition of 1,25D synthesis also led to an increase in renin expression, whereas 1,25D injection led to renin suppression. Vitamin D regulation of renin expression VDR activators could help prevent or ameliorate hypertension.

It is suggested to test for and treat reduced 25(OH)D concentrations with natural vitamin D: this therapy is safe, cheap and simple, reduces PTH levels and might also reduce cardiovascular events and mortality.

Reports based on observational data have noted improved outcomes with active vitamin D treatment (calcitriol, paricalcitol, alfacalcidol, or doxercalciferol) in patients with CKD. Criteria for identification of active vitamin D treatment failure are unclear from current guidelines, although up to 50% of patients may experience treatment failure eventually because of development of hypercalcemia or resistant SHPT, characterized by an elevated intact PTH (iPTH) level despite treatment.

Is there any place left for active vitamin D?

Mario Cozzolino

The triad composed of basic and clinical research, promoting disease prevention, and education is and will remain the mantra of our association for the years ahead.

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Can we recover klotho in CKD?

In chronic kidney disease (CKD) patients, accelerated skeletal, renal and cardiovascular aging markedly increases their risk for bone fractures, end-stage kidney disease and cardiovascular mortality. The serendipitous discovery of α-klotho, a bona fide anti-aging molecule expressed mainly in the kidney, has provided a ‘single cause-effect link’ between CKD progression and accelerated aging. In mice, α-klotho is the only gene whose mutation causes short lifespan/ premature aging, osteoporosis, soft tissue calcification and arteriosclerosis. Furthermore, exclusive ablation of renal klotho results in the multiple organ injury of human aging, indistinguishable from that observed upon global α-klotho ablation. Because CKD is the most powerful down-regulator of renal α-klotho content, this talk is focusing on the pathophysiology underlying a major limitation to design safe strategies to recover renal klotho in CKD: the lack of accurate biomarkers to reflect renal α-klotho expression and function. Specifically, renal α-klotho anti-aging actions involve the distinct activity of two α-klotho isoforms: in proximal tubules, a transmembrane α-klotho protein acts as a co-receptor for the FGF23/FGFR complex to induce phosphaturia by decreasing the expression and activity of sodium-phosphate co-transporters. In turn, the resulting amelioration of renal phosphate retention by the injured kidney attenuates secondary hyperparathyroidism, CKD progression, systemic inflammation and vascular calcification. The kidney is also the main source of circulating and urinary soluble α-klotho, a shorter α-klotho molecule generated by proteolytic cleavage of the extracellular domain of transmembrane α-klotho and, also, through alternative splicing of the α-klotho gene. Soluble α-klotho functions as an endothelium anti-aging molecule: while the anti-oxidant, anti-apoptotic, anti-fibrotic, anti-senescence properties of circulating soluble α-klotho result in multimolecular protection, urinary soluble α-klotho induces FGF23-independent phosphaturia by impairing the membrane localization of sodium-phosphate co-transporters. Transgenic overexpression studies in experimental CKD have demonstrated that α-klotho repletion attenuates pathological cardiac remodeling. However, while α-klotho repletion can only limit rather than reverse renal fibrosis, preserving renal function, strategies to correct the three main downregulations of renal α-klotho/soluble α-klotho that associate with the lowest mortality risk, in the course of CKD.

An explanation for these discrepancies emerged with the identification of the critical role of the kidney in the transcytosis of circulating soluble α-klotho into the urinary space. Since the size of circulating α-klotho impedes its glomerular filtration, accumulation of soluble α-klotho in the circulation due to a defective transcytosis through the damaged kidney into the urine could mask CKD-induced reductions in renal α-klotho content. Alternatively, nonrenal sources could contribute to circulating soluble α-klotho under non-physiological conditions. In fact, immune cells could be shedding soluble α-klotho, as their endogenous klotho content decreases during inflammatory states causing immunological aging. Therefore, nephrologists interested in preserving renal α-klotho content in CKD are currently limited to correct the three main downregulations of renal α-klotho content, namely, vitamin D or calcitriol deficiency, hypertension and systemic inflammation. Activation of the vitamin D receptor directly induces the expression of the α-klotho gene. Indeed, administration of active vitamin D analogs increased endogenous α-klotho levels and decreased vascular calcification in rodent CKD models, and reduced mortality rates in dialysis patients bearing a polymorphism of the α-klotho gene that imparts its pro-survival function. However, while the correction of vitamin D deficiency at early CKD stages could safely attenuate reductions in renal α-klotho, the development of hyperphosphatemia precludes the use of this strategy to improve the severely low renal klotho content of advanced CKD. Strategies directed to attenuate the activation of the renin-angiotensin system could also effectively counteract hypertension-driven reductions of renal α-klotho.

Lastly, in severe rat CKD with hyperphosphatemia, the FDA-recommended dietary intake of anti-inflammatory barley β-glucans, sufficed to significantly attenuate renal α-klotho reductions, which associated with improved renal function, reduced renal inflammatory cell infiltration, reduced aortic TNFα gene expression and a 50% reduction in aortic calcification. These outcomes were all unrelated to improvements in serum phosphate levels or in bone and mineral metabolism.

The prospective clinical trials required to assess the safety and efficacy of novel strategies to preserve renal α-klotho in human CKD await the identification of optimal biomarkers of the expression and function of the renal α-klotho/soluble α-klotho axis.
When chronic kidney disease (CKD) progresses to end-stage renal disease, the risk of cardiovascular mortality increases exponentially and occur at a much younger age. Few other patient groups display such a marked discrepancy between chronological and biological age as patients with CKD. Thus, it has been suggested that CKD could be used as a clinical model to study premature vascular aging processes [1].

In the uremic milieu several factors promote premature aging, such as increased allostatic load (inflammation and oxidative stress), specific pro-aging factors (hyperphosphatemia, angiotensin 2 and sodium accumulation) and defective anti-aging protective mechanisms (such as klotho and vitamin D deficiency and nuclear lamina defects) promote a phenotypic progeric. Metabolic vascular calcification (VC) is a distinct feature in CKD that associate with arterial stiffness and predicts poor cardiovascular outcome. It is well established that osteogenic factors, such as matrix Gla protein (MGP) and runt-related transcription factor 2 (RUNX2), are part of the arterial calcification process.

By detailed studies of arterial biopsies we have recently published a manuscript [2] on the impact of senescence on the vascular progenitor phenotype in CKD. Proteins derived from the cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) are functionally involved in maintaining cells in a state of growth arrest. Since cellular senescence increases with age, expression of CDKN2A increases as a function of increasing cellular stress and organismal aging and appears to be superior to telomere length as a biomarker of biological age. In other patient groups elevated CDKN2A expression correlates with increased biological age as well as increased frequency of a frail phenotype. A key feature of cellular senescence is the senescence-associated secretory phenotype (SASP), which results in the secretion of pro-inflammatory factors that poison the tissue in the proximity of the senescent cell. It has been documented that the SASP impact stem cell mobilisation and nitric oxide secretion, promote the invasion of monocytes and cause endothelial leakiness. Based on 61 arterial biopsies we report strong association between degree of VC, SASP and the expression of CDKN2A/p16\(^{\text{INK4a}}\), MGP and RUNX2. These observations are supported by the increased number of p16\(^{\text{INK4a}}\) and SAβ-Gal positive cell in arteries with severe VC. The underlying cause(s) of the increase in CDKN2A/ p16\(^{\text{INK4a}}\) expression in the uremic milieu are understood, Prelamin A expression promotes calcification and ageing in VSMCs – an effect which appears to be mediated, at least in part, by p16 protein. In addition, RUNX2 may be activated by Prelamin A and DNA damage signalling, further linking cellular stress, p16 activity and an osteogenic potential. Another possibility for increased p16\(^{\text{INK4a}}\) expression in ESRD is impairment of immune system function. Indeed, p-cresylsulphate induces macrophage activation, which lead to a failure in adaptive immune response. Taken together, we report that increased arterial expression of CDKN2A/p16\(^{\text{INK4a}}\) associated with vascular progenia in the uremic milieu, independently of chronological age [2]. Since senescent cells have been considered a target for anti-aging therapies and removal of p16\(^{\text{INK4a}}\)-positive cells in progeric mice led to an attenuation of the ageing phenotype, a functional involvement of p16\(^{\text{INK4a}}\) in ageing-associated disorders is likely. Thus, based on our observations the use of SASP modulators and/or senolytic drugs are intriguing prospect for the future treatment of uremic vascular progenia.

References

Should we stop ACEI/ARBs in stage 5 CKD?

We should practice personalized and precision medical care in these patients

Chronic kidney disease (CKD) (stages 3 – 5) is a global health issue and is associated with high risk of overall mortality and almost 50-fold higher risk of end-stage renal disease (ESRD) compared to age-matched individuals with presumed normal renal function. Advanced CKD (stages 4 and 5) has a major negative impact on a range of clinical outcomes including quality of life, and carries a high economic burden, either through cardiovascular or metabolic bone disease or due to the high cost of dialysis.

Irrespective of the underlying cause of CKD, attention has mainly been focused on blood pressure (BP) control and reduction of proteinuria using ACEI and/or ARBs in order to allegedly lower intraglomerular pressure over and above their effect on systemic BP. Several landmark studies including meta-analysis have confirmed the benefits of ACEI or ARBs, particularly when used in proteinuric patients with mild to moderate CKD. However, the rigor of or some of these studies, which failed to disassociate renoprotection from any hypertensive effects of ACEI/ARBs, is now being questioned. Particularly in non-proteinuric patients (proteinuria < 1 g/d)

New mechanisms of cardiac fibrosis and failure in CKD

It is now recognized that a hallmark cardiac lesion found in the left-ventricular (LV) myocardium of patients with chronic cardiac conditions is the diffuse deposition of collagen fibers, namely type I, within the interstitium of the cardiac muscle (myocardial interstitial fibrosis or MIF). In the context of diverse cardiac and non-cardiac diseases, a number of mechanical, humoral and metabolic stimuli induce the differentiation of cardiac fibroblasts into myofibroblasts that secrete excessive collagen, as well as molecules that alter the extracellular processing of collagen. This leads to the formation of highly cross-linked, stiff collagen type I fibers that are resistant to degradation.

The functional impact of MIF in cardiac patients is a matter not only of the quantity (i.e. severity of deposition), but also of the quality of collagen type I fibers (i.e. the degree of cross-linking among collagen type I fibrils). For instance, greater collagen-dependent myocardial stiffness responsible for LV diastolic dysfunction is associated with increased myocardial content of highly cross-linked collagen type I in patients with heart failure with preserved fraction (HFpEF).

Recent data suggest that in patients with HFpEF, cystatin C is increased and is associated with diastolic dysfunction independent of glomerular filtration rate. In addition, experimental data suggest that an excess of cystatin C might contribute to diastolic dysfunction in HFpEF via alterations in the extracellular processing of collagen by cardiac fibroblasts. Therefore, cystatin C-mediated MIF may represent a novel pathogenic link between the kidney and the heart, particularly in conditions in which LV diastolic dysfunction or HFpEF and chronic kidney disease coexist in the same patient.

Cystatin C-mediated myocardial interstitial fibrosis: a novel pathogenic link between the kidney and the heart

Session 5.3
Residual renal function in HD – an opportunity for improvement
Monday, 11.45 – 13.15, Hall 10.A

Session 4.1
Chronic kidney disease – a clinical model of premature ageing
Monday, 11.45 – 13.15, Hall 1103 – 104

Session 3.8
Fibrosis complicating several scenarios in chronic kidney disease
Monday, 15.15 – 16.45, Hall N105 – 106

E-ISSUE
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The proportion of the elderly in the world population is increasing, bringing with it an increased prevalence in age-related morbidities. By 2050, those over 60 years old will outnumber those below age 14 years and constitute 2 billion of the world’s population. Consequently, the World Health Organization (WHO) places increased emphasis on promoting better age-related functional health.

Studies are promising, but important caveats must be resolved before clinical use

Presently, there is no gold standard for determining what constitutes normal aging. Increasing chronological age results in a loss of physiological function and is accompanied by systemic low-grade inflammation. Notably, the incidence of CKD parallels chronological aging and almost 30% of ESRD patients are 65 years or older. Accelerated ageing is already an established underlying component renal dysfunction in CKD. Correspondingly, CKD patients exhibit vascular progeria and show a higher incidence of mortality in comparison to healthy chronologically age-matched individuals. Therapeutic intervention to address this acceleration in aging may now be feasible.

Geroscience comprises an interdisciplinary effort that has improved our understanding of the relationship between aging and age-related diseases. It has generated significant insight into interventions and modifications to enable healthier old age that would also be expected to affect a broad range of age-related morbidities. It has provided a range of evidence suggesting that aging can be ‘drugged’ and that health span can be improved. Studies in a range of model organisms have identified several key pathways relevant to ageing processes across taxa (i.e. in yeast, worms, mice and man) that are amenable to intervention using current clinical therapeutics.

Targeting and modification of the activity of the mTOR pathway by metformin, rapamycin, or rapamycin analogues (rapalogues) has already improved health span in mice and produced evidence suggesting that aging can be ‘drugged’ and that health span can be improved. Studies in a range of model organisms have identified several key pathways relevant to ageing processes across taxa (i.e. in yeast, worms, mice and man) that are amenable to intervention using current clinical therapeutics.

Targeting/Taming Aging With Metformin (TAME) study. The rapalogue RAD001 has also shown some initial promise at combating immuno-se-nescence in man.

Another promising molecule is resveratrol, a naturally occurring polyphenol found in a range of berries and in red wine. Resveratrol has been demonstrated to enhance the activities of simian family members, which are regulators of cellular stress and metabolism. Long-term use of resveratrol increases lifespan in mammals and has been shown to improve metabolic rate and muscle function in humans.

A number of drugs targeting the activities of Klotho, FGF-21, PAPP-A, are also showing promise in combating the effects of aging in man, potentially via modulation of insulin-signaling pathways. In rodents, overexpression of FGF-21 and Klotho improved health span and increased longevity by 36% and 31% respectively. Conversely, Klotho knock-out induced progeria.

Recently, a range of senolytic drugs, which selectively eliminate senescent cells from tissues and organs, has been demonstrated to improve health span with great effect in mice. Senescent cells are resistant to apoptosis and senolytic drugs, such as dasatinib, quercetin, navitoclax, among others, inhibit the pathways upregulated in senescent cells that confer their apoptosis resistance. Removal of these cells thus improves organ function and facilitates tissue repair.

Finally, simple dietary manipulation can improve health span and increase lifespan. An example of this is dietary methionine restriction, which is sufficient to improve health span in rodents, where its benefits are derived from activation of the trans-sulfuration pathway resulting in improved cellular metabolism.

Some caveats remain, in any attempt to ‘drug aging’. Of note, such treatments that may be benign in controlled studies in a laboratory or clinical setting, may have adverse effects on health and lifespan when they are exposed to the heterogeneity of a general population and subject to psychosocial, nutritional and lifestyle confounders. Any benefits may be thus be context dependent. Any such therapeutic agents will therefore need to be investigated across the life course, to determine if their effects are uniform, or even reversible, over time, or if they demonstrate effects subject to antagonistic pleiotropy. Cellular senescence may well fit the context of this bill, being undesirable early in the life course, but desirable later to prevent cancers.

Can aging be drugged?

The proportion of the elderly in the world population is increasing, bringing with it an increased prevalence in age-related morbidities. By 2050, those over 60 years old will outnumber those below age 14 years and constitute 2 billion of the world’s population. Consequently, the World Health Organization (WHO) places increased emphasis on promoting better age-related functional health.

Studies are promising, but important caveats must be resolved before clinical use

Presently, there is no gold standard for determining what constitutes normal aging. Increasing chronological age results in a loss of physiological function and is accompanied by systemic low-grade inflammation. Notably, the incidence of CKD parallels chronological aging and almost 30% of ESRD patients are 65 years or older. Accelerated ageing is already an established underlying component renal dysfunction in CKD. Correspondingly, CKD patients exhibit vascular progeria and show a higher incidence of mortality in comparison to healthy chronologically age-matched individuals. Therapeutic intervention to address this acceleration in aging may now be feasible.

Geroscience comprises an interdisciplinary effort that has improved our understanding of the relationship between aging and age-related diseases. It has generated significant insight into interventions and modifications to enable healthier old age that would also be expected to affect a broad range of age-related morbidities. It has provided a range of evidence suggesting that aging can be ‘drugged’ and that health span can be improved. Studies in a range of model organisms have identified several key pathways relevant to ageing processes across taxa (i.e. in yeast, worms, mice and man) that are amenable to intervention using current clinical therapeutics.

Targeting/Taming Aging With Metformin (TAME) study. The rapalogue RAD001 has also shown some initial promise at combating immuno-se-nescence in man.

Another promising molecule is resveratrol, a naturally occurring polyphenol found in a range of berries and in red wine. Resveratrol has been demonstrated to enhance the activities of simian family members, which are regulators of cellular stress and metabolism. Long-term use of resveratrol increases lifespan in mammals and has been shown to improve metabolic rate and muscle function in humans.

A number of drugs targeting the activities of Klotho, FGF-21, PAPP-A, are also showing promise in combating the effects of aging in man, potentially via modulation of insulin-signaling pathways. In rodents, overexpression of FGF-21 and Klotho improved health span and increased longevity by 36% and 31% respectively. Conversely, Klotho knock-out induced progeria.

Recently, a range of senolytic drugs, which selectively eliminate senescent cells from tissues and organs, has been demonstrated to improve health span with great effect in mice. Senescent cells are resistant to apoptosis and senolytic drugs, such as dasatinib, quercetin, navitoclax, among others, inhibit the pathways upregulated in senescent cells that confer their apoptosis resistance. Removal of these cells thus improves organ function and facilitates tissue repair.

Finally, simple dietary manipulation can improve health span and increase lifespan. An example of this is dietary methionine restriction, which is sufficient to improve health span in rodents, where its benefits are derived from activation of the trans-sulfuration pathway resulting in improved cellular metabolism.

Some caveats remain, in any attempt to ‘drug aging’. Of note, such treatments that may be benign in controlled studies in a laboratory or clinical setting, may have adverse effects on health and lifespan when they are exposed to the heterogeneity of a general population and subject to psychosocial, nutritional and lifestyle confounders. Any benefits may be thus be context dependent. Any such therapeutic agents will therefore need to be investigated across the life course, to determine if their effects are uniform, or even reversible, over time, or if they demonstrate effects subject to antagonistic pleiotropy. Cellular senescence may well fit the context of this bill, being undesirable early in the life course, but desirable later to prevent cancers.
Optimizing RAASi therapy in cardio-renal patients through hyperkalaemia management

Chair: Professor Angel de Francisco

Monday 5 June 2017
13:30–15:00

Hall 10.A, IFEMA Feria de Madrid
(North Congress Centre)

PROGRAMME

13:30  Lunchboxes will be provided

13:45  Chair’s welcome and introduction
       Angel de Francisco (Spain)

13:50  RAASi benefit: Slowing down kidney function decline
       Professor Stefan Anker (Germany)

14:10  Hyperkalaemia management: Current limitations
       and unmet needs
       Professor Patrick Rossignol (France)

14:30  Changing the treatment paradigm in hyperkalaemia management
       Professor David Bushinsky (USA)

Closing remarks and Q&A
       Angel de Francisco
Endoglin and ALK1: their role in kidney fibrosis

Independent of the initial causes of chronic kidney disease (CKD), final stages of CKD are characterized by an increase of extracellular matrix (ECM) in either the glomeruli (glomerulosclerosis), the tubular interstitium (interstitial fibrosis) or in type I receptors, such as β1 in renal fibrosis, which facilitates the study of genetic and environmental scenarios in chronic kidney disease.

In addition, there is another member of the TGF-β receptor complex, endoglin, a membrane glycoprotein that regulates TGF-β-induced signaling and its biological effects. It has been reported that endoglin expression is increased in the renal interstitium of diseased human kidneys, compared with healthy kidneys. Thus we assessed the possible role of endoglin in renal fibrosis. Several studies from our laboratory have demonstrated that endoglin is upregulated in experimental models of kidney fibrosis, whereas endoglin overexpression in cultured cells is associated with reduced expression of ECM proteins and a reduction in collagen production.

In order to evaluate kidney fibrosis regulation in vivo, we used a model of unilateral ureteral obstruction (UUO). This simple and reliable model has been described as being mediated by recruitment of ECM molecules in fibrosis. In an early paper, we observed that endoglin-dependent Smad1 and Smad3 phosphorylation and binding to Smad4, and this Smad complex regulates gene promoters in a different and sometimes opposite way from Smad2/3. Moreover, Smad1/5/8 and Smad2 proteins show lateral antagonism due to their competition for Smad4 to form the Smad complex.

In conclusion, we suggest that Endoglin-ALK1 receptor complex plays an important role in the regulation of ECM protein expression, proliferation and migration in fibroblasts, and that this complex could be a potentially powerful anti-fibrotic target.

References
1. Roy-Chaudhury P et al. Exp Nephrol 1997; 5:
Advanced care planning (ACP) was historically considered as a finite exercise, in which a patient completed some written documents after a conversation with his or her physician. The documents consisted of a proxy directive and various instruction directives on general wishes about care at the end of life, or specific directives or living wills concerning interventions the patient would or would not accept (for example, cardiopulmonary resuscitation, prolonged ventilation orders and physician orders for life-sustaining treatment).

However, we now know that ACP is a much more comprehensive and dynamic patient-centered process of reflection and discussion between a patient, his or her family and healthcare providers for the purpose of clarifying values, treatment preferences, and goals of end-of-life care. ACP is a patient-centered initiative that promotes shared decision-making, and which may include completion by the patient of an advance directive that documents his or her wishes and/or the appointment of a substitute decision maker. But ACP is not just about old age. At any age, a medical crisis could leave someone too ill to make his or her own healthcare decisions.

Dialysis therapy in elderly dependent patients is accompanied by a high mortality and a progressive deterioration in functional status. These poor results are responsible for the increase in the percentage of patients who discontinue dialysis. Therefore, before starting kidney replacement therapy, there should be a shared decision-making process on the basis of the understanding of the prognosis, the potential benefits and harms of therapy, and the patient’s values, goals, and preferences.

Despite specific legislation, only a small percentage of patients on dialysis have had access to an ACP process. However, when patients are asked about their desires, a high percentage really want to make a choice about any interventions in case of unresolved coma, permanent vegetative state, irreversible dementia, or serious non-treatable disease. As nephrologists, we should assume our responsibility for the low implementation of the ACP process. The use of structured communication tools may increase the frequency of discussions about, and completion of, advance directives, and concordance between the care desired and the care received by patients. Some studies have shown that educational interventions to train healthcare professionals in end-of-life communication have significantly improved the results. We also need validated prognostic scores. Current prognostic tools are not sensitive or specific enough to tell a patient how long they will live, though they are informative in identifying high-risk populations. We need more complex models that include disease conditions, treatments, outcomes and functional conditions to enable a better diagnostic approach in patients with chronic kidney disease (CKD) or of older age.

Finally, efforts to promote interdisciplinary collaboration among the diverse providers who care for patients with advanced kidney disease will likely be needed to promote effective ACP in this population.
The Sasaki group first demonstrated the crucial role of high uric acid levels as a risk factor for the development and progression of kidney disease was first proposed almost a century ago. Findings from experiments in animals and humans epidemiologic studies suggest that uric acid plays a causal role in hypertension, cardiovascular disease, and kidney disease. In rats, hyperuricemia induced by oxonic acid leads to primary hyperuricemia and renal disease. In a five-year follow-up of 28,283 children in 55 epidemiologic study from California, high uric acid levels appeared to be a major risk factor for end-stage renal disease. In addition, hyperuricemia was an independent risk factor for faster progression of chronic kidney disease (CKD) in children and adolescents in an epidemiologic study of 891 children in 55 pediatric nephrology centers across North America. However, not all studies have shown a association between hyperuricemia and renal outcomes. In a sub study of the Modification of Diet in Renal Disease study, a randomized controlled trial including 840 CKD patients, hyperuricemia appeared to be an independent risk factor for all-cause and cardiovascular mortality, but not for kidney failure. Genetic studies of hyperuricemia and gout, and the influence of these conditions on renal outcomes and cardiovascular risk factors are controversial. Most of the genes that are associated with serum uric acid levels and gout are involved in the renal urate transport system. Meta-analyses of genome-wide association studies were performed in 5 population-based cohorts of the CHARGE consortium for serum urate and gout in 28,283 white individuals. Adjusted serum urate was strongly associated with all of the cardiovascular disease risk factors examined. In contrast, the genetic urate risk score was not associated with systolic blood pressure, diastolic blood pressure, estimated glomerular filtration rate (eGFR), or CKD. However, a study from the Zuccoli group found an association between a polymorphism in a gene encoding a urate transporter (GLUTUR) and progression of CKD. A GLUTUR polymorphism, strongly associated with serum uric acid levels in healthy individuals in the general population with normal renal function, is highly predictive of progression of kidney disease. These findings are compatible with the hypothesis that uric acid may play a role in progression of kidney disease. Several interventional studies have analyzed the effect of lowering uric acid levels on progression of kidney disease. The angiotensin-receptor anagontist losartan has uricosuric properties. In a subanalysis of the RENAA study, the risk reduction for incident renal outcomes (doubling of serum creatinine or end-stage renal disease) was 6% per 0.5 mg/dL decrease in serum uric acid. The xanthine oxidase inhibitor febuxostat slowed the decline in eGFR in CKD patients in a short-term, 6-month, double-blind controlled study. A member of our group, Dr. Goicoechea, studied the effect of lowering uric acid levels with allopurinol in patients with progressive CKD and cardiovascular risk. A total of 113 patients with CKD, eGFR <60 ml/m² per 1.73 m², a stable clinical condition, and a mean baseline serum uric acid level of 7.6 mg/dl were randomized to allopurinol 100 mg/d or placebo. In comparison with the control group, allopurinol reduced uric acid levels, inflammation parameters such as C-reactive protein, and albuminuria. In the allopurinol group, there was no significant change in eGFR after 24 months, whereas in the control group there was worsening by the end of the study. Allopurinol slowed progression of kidney disease (defined as a decrease higher than 0.2 ml/min/1.73 m² per month) by 50% compared with control groups in a Cox regression model. Furthermore, allopurinol reduced the risk of cardiovascular events by 71% compared with standard therapy. In a post hoc analysis including long-term follow-up for an additional five years, this beneficial effect was maintained by corroborating the beneficial effect of decreased uric acid level on progression of CKD. Further support that allopurinol decreases blood pressure and creatinine levels in patients with hyperuricemia was found in a recent meta-analysis of randomized controlled trials with the keywords (continued on page 18)
Research Collaboration in the DOPPS Program: Optimizing care in advanced CKD and the transition to dialysis

The Dialysis Outcomes and Practice Patterns Study (DOPPS) began in 1996 as a prospective cohort study of hemodialysis (HD). From the outset, the goal of the study has been to better understand HD facility practices that are strongly associated with outcomes for HD patients and inform best practices in HD care. The DOPPS Program continues to grow and has included the participation of 23 countries, including Australia, Bahrain, Belgium, Brazil, Canada, France, Germany, Italy, Japan, Kuwait, New Zealand, Oman, Qatar, Russia, Saudi Arabia, Spain, Sweden, Thailand, Turkey, United Arab Emirates, United Kingdom, United States, and China (large metropolitan regions of Beijing, Guangzhou, and Shanghai). A key principle in the design of the DOPPS Program is to collect extensive detailed patient-level and facility-level data and employ statistical modeling approaches that strive to minimize treatment by indication bias. The ultimate goal of the DOPPS Program through these efforts is to lead to improvements in care that allow patients to live longer with better quality of life.

Based on DOPPS successes in hemodialysis, additional studies of chronic kidney disease (CKD) and peritoneal dialysis (PD) patients have been launched. These studies share similar goals and design principles as the hemodialysis study. The Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) studies patients with advanced CKD (estimated glomerular filtration rate [eGFR] < 45 mL/min/1.73 m²) followed at nephrology clinics. The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) was designed to identify predictors of PD technique survival.

Since its inception in 1996, the DOPPS Program has published more than 200 papers covering a broad spectrum of HD practices, based upon nationally representative samples of HD facilities and patients in each country. Examples of the breadth of DOPPS research published during the last several months include international papers on hepatitis C infection in patients on HD, dialysate potassium and serum potassium in HD, interdialytic weight gain, and a methods paper on use of observational data in HD research. From the beginning, DOPPS research has had a special focus on patient self-reporting of many different experiences while receiving chronic hemodialysis therapy for kidney failure.

The DOPPS Program is made possible through generous support by a consortium of biopharmaceutical and government sponsors, who provide their support without restrictions on publications. Furthermore, it is the many contributions and devoted efforts of more than 100 investigators, study team members, clinical research associates, hundreds of dialysis unit staff, and more than 60,000 patient participants across 23 countries, who together provide findings from the DOPPS Program to help inform care for advanced CKD and dialysis patients worldwide. The DOPPS Program is honored and very appreciative of the opportunity once again to share these international findings with attendees of the ERA-EDTA Congress in an interactive session that we hope encourages and nurtures opportunities for new research directions.

In the first part of this session, Dr Hugh Rayner will provide an overview of the DOPPS Program and extend an invitation to those wishing to collaborate on future research projects. The DOPPS Program 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. Visit www.DOPPS.org to learn more about opportunities for collaboration.

CKDopps: Improving outcomes in advanced CKD and the transition to dialysis

CKD, even in its early stages, is associated with an increased risk of cardiovascular events and progression to end stage renal failure. As we know from the DOPPS, mortality rates reach the highest level after dialysis start, indicating that transition to dialysis is the most vulnerable phase in the treatment of CKD. The goal of the CKDopps is to study variations in advanced CKD practices and to identify nephrologist practices associated with better patient outcomes for moderate and advanced CKD patients.

Dr Helmut Reichel will give an overview of the CKDopps and study findings relating to transition into dialysis. In this ongoing international prospective cohort study, national samples of nephrology clinics in Brazil, France, Germany, Japan, and the United States are enrolled. Descriptive data will demonstrate important variations in practice across countries. Patient characteristics at the time of transition into dialysis will be described in order to address key questions, such as the problem of identifying the optimal timing of dialysis start, and best practices to optimize dialysis access use at this start. Furthermore, differences in practices will be investigated by patient characteristics and preferences.

DOPPS: Impact of clinical practices on early mortality among HD patients

The period soon after the start of dialysis is recognized as a critical time for patients with CKD. Patients are more vulnerable physically and psychologically, and are just beginning to adapt to this lifelong treatment. A study based on the United States cohort of the DOPPS found that this high mortality period after HD initiation extends through the first 120 days of treatment. This study also identified the factors associated with elevated mortality early after the initiation of HD.

Dr Takeshi Hasegawa will discuss these findings and provide further details about subsequent studies examining the prevalence of pre-dialysis nephrologist care, which varied not only by country but also by facility. These variations helped to answer questions about the possible benefit of increased attention to pre-dialysis nephrologist care as a modifiable determinant of early mortality and quality of life among HD patients.

PDOPPS: Predictors of early successful PD use

The PDOPPS is a multinational collaborative study currently involving seven countries (United States, Canada, Japan, Australia, United Kingdom, New Zealand, and Thailand) with the primary aim of better understanding modifiable causes of technical failure. Its workgroups include the clinical application of PD therapy, catheter access and function, infection prevention and management, dialysis prescription and fluid management, patient training and education, and patient support.

Currently 210 facilities are actively participating in the study, with 9630 patients so far consented. It is by far the largest cohort PD study conducted to date. The patient involvement group has specifically explored aspects of modality choice, and quality of life is also reported. A sub-study in the United Kingdom (UK CatM) explores the relationship between PD outcomes associated with surgical and medical insertion pathways. Genetic influences on peritoneal membrane function are the subject of a further sub-study (BioPD).

Dr Martin Wilkie will discuss early results of the PDOPPS study, including variations in peritonitis rates and infecting organisms, infection-associated hospitalization and catheter removal, and differences in training practices and preventative measures between countries.

Recent results from the EURODOPPS

The EURODOPPS is a collaborative venture between the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) and Arbor Research Collaborative for Health. The aims of the project are to aid European investigators in analyzing epidemiological data on patients receiving hemodialysis in seven European countries (Germany, Italy, France, United Kingdom, Belgium, Spain, and Sweden) to address scientific and policy-related questions.

In the three years since its conception, the EURODOPPS initiative has provided an opportunity for seven European investigators to analyze the EURODOPPS data, culminating in eight projects from two calls for research proposals. With nearly all research projects from the first call coming to completion, the EURODOPPS celebrated its first publication in Nephrology Dialysis Transplantation at the beginning of 2017.

Dr Ayesha Sajjad, the EURODOPPS study coordinator, will provide an update on the progress of the EURODOPPS and will further highlight interesting results from some ongoing research projects.
The EURODOPPS is a collaborative venture between ERA-EDTA and Arbor Research Collaborative for Health. Among the aims of the project are to support European investigators to analyze epidemiological data provided by DOPPS study on patients receiving hemodialysis in seven European countries (Germany, Italy, France, United Kingdom, Belgium, Spain, and Sweden) included in the study, and to address scientific and policy-related questions. Moreover, ERA-EDTA largely supported the collection of the data in different new DOPPS waves to update the follow-ups.

Recent results from EURODOPPS – New publications and ongoing research using EURODOPPS data

In the three years since its conception, the EURODOPPS initiative has provided the opportunity for seven European investigators to analyze the EURODOPPS data, culminating into eight projects from two calls for research proposals. With nearly all research projects from the first call coming to their completion, the EURODOPPS celebrated its first publication by Sophie Liabeuf et al. on the relationship between attainment of guideline targets and a country’s healthcare expenditure and nephrologist workforce [1]. Another paper on geographical variations in blood-pressure level and seasonality by Flore Duranton et al. has been submitted for publication.

On 5th June during the DOPPS Symposium, Dr. Ayeshah Sajjad, the EURODOPPS study coordinator, will provide an update on the progress of the EURODOPPS and will further highlight on some interesting results from ongoing EURODOPPS research projects. The aims of one project are to determine whether longer hemodialysis session treatment time delivered three times a week reduces mortality and hospitalization on the first day after the two-day break in patients receiving three times a week hemodialysis. The results of this study suggest that, despite overall reductions in mortality and hospitalization, these events are still more frequent at the first day after the two-day break compared to the rest of the week in patients performing longer dialysis treatment times three times a week.

Another EURODOPPS project aimed to assess the risk of death and hospitalization according to the levels of guideline attainment. Different international guidelines have focused on reducing chronic kidney disease (CKD) complications. In hemodialysis patients, the role of an optimal attainment of different targets proposed by the guidelines for CKD care for better survival remains largely unexplored. The EURODOPPS data aided the determination of survival and hospitalization rates in patients according to the simultaneous attainment of different targets for hypertension, anemia and CKD-mineral bone disease.

Treatment of hyperglycemia in chronic kidney disease

Intensified, multifactorial intervention in type 2 diabetic patients with microalbuminuria, including improving glycemic control, treating blood-pressure with blockade of the renin–angiotensin system, treating with statins and implementing lifestyle interventions shows progression in nephropathy and renal function loss, thereby reducing the risk of end-stage renal disease (ESRD). This was recently confirmed in a 21-year follow-up of the so-called Steno-2 Study. Such multifactorial intervention has now been used in most countries for decades. It has had a beneficial stabilizing effect on the previously observed marketed annual increase of diabetic patients progressing to ESRD. In the same period it has been very difficult to demonstrate a beneficial effect of improving glycemic control per se on survival and/or progression to ESRD. For many years it was said that only metformin had such an effect. This was shown in the UKPDS study, but the effect was indeed only shown in a very small subgroup of patients and only in patients who could manage their diabetes with metformin alone. Despite of this relatively weak documentation, metformin is the preferred first-line glucose-lowering drug in type 2 diabetic patients. In a Clinical Practice Guideline from ERA-EDTA published in 2015 it was suggested that metformin is so valuable that it should be used even in patients with CKD 3b or worse if care is taken to inform patients about stopping the drug during certain acute events in order to minimize the potential risk of lactic acidosis. More recently, new treatment principles with new drugs have been introduced:

- First, drugs that increase the endogenous insulin production using the incretin hormone function of glucagon-like-peptide 1 (GLP-1), by either inhibiting the degradation of the endogenously produced GLP-1 by blocking the degrading enzyme DPP-4 (DPP-4 inhibitors) or by using slowly degraded analogues (GLP-1 analogues).
- Second, drugs that block sodium-glucose cotransporter 2, the so-called sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors). These drugs basically lower blood glucose by reducing the renal reabsorption of glucose, thereby increasing urinary glucose excretion.

When these drugs were introduced for clinical use, many of us saw only little or no use for them accompanied by an eGFR below 45 ml/min per 1.73 m²; the initiation of renal replacement therapy; or death from renal disease. It was shown that, when added to standard care, empagliflozin was associated with slower progression of clinically relevant renal events compared to placebo.

The LEADER trial randomized 9340 type 2 diabetic patients with high cardiovascular risk to receive the GLP-1 analogue liraglutide or placebo. They had to be in CKD stage 3 or better. The rate of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke was lower with liraglutide than with placebo. The incidence of a composite outcome of renal or retinal microvascular events was lower in the liraglutide group than in the placebo group. This difference was driven by a lower rate of nephropathy events, such as new-onset persistent microalbuminuria, in particular in the liraglutide group.

The SUSTAIN trial randomized 3297 patients with type 2 diabetes who were at high cardiovascular risk to receive once-weekly semaglutide, a long-acting GLP-1 analogue, or placebo for 104 weeks. The hypothesis was that semaglutide would be non-inferior to placebo for the primary outcome, which was the first occurrence of cardiovascular death, nonfatal MI or nonfatal stroke. The patients had to be in CKD3 or better. The non-inferiority of semaglutide was demonstrated, since the rate of patients reaching the primary outcome was significantly lower in the semaglutide group than among those receiving placebo. Among the prospectively specified secondary outcomes were new or worsening nephropathy, which was observed in 62 patients (3.3%) in the semaglutide group and 100 (6.1%) in the placebo group (p < 0.05).

Based on these studies, new guidelines on treatment of type 2 diabetes recommending the use of empagliflozin and liraglutide as second line to metformin and insulin are emerging. This is because of the apparent cardiovascular benefits and because these drugs have been shown to be safe in CKD3 or better, possibly providing a benefit on progression of nephropathy. More studies on other drugs are ongoing. We will soon need new guidelines for glucose lowering in patients with CKD3 – 5 based on new evidence from these studies.

References

We will soon need new guidelines based on results from clinic trials

In patients with chronic kidney disease (CKD), recent publications of larger-scale trials in NEJM in 2016 showed that apparently we were wrong. The SGLT2 inhibitor empagliflozin and the GLP-1 analogues liraglutide and semaglutide all showed direct effect or non-inferiority regarding death and progression of nephropathy. The three clinical studies will now briefly be summarized.

The EMPA-REG OUTCOME trial included 4124 type 2 diabetic patients with established cardiovascular disease. They had an eGFR of 30 ml/min per 1.73 m² (i.e. CKD3 or better) and were randomized to receive either the SGLT2 inhibitor empagliflozin or placebo. Among the secondary outcomes were: incident or worsening of nephropathy; a doubling of the serum creatinine level

fits and because these drugs have been shown to be safe in CKD3 or better, possibly providing a benefit on progression of nephropathy. More studies on other drugs are ongoing. We will soon need new guidelines for glucose lowering in patients with CKD3 – 5 based on new evidence from these studies.
Is HbA1c the optimal biomarker of glycemic control in CKD?

Defining an appropriate glycemic target in a diabetic patient is the cornerstone of the prevention and treatment of the complications of diabetes mellitus. In 1993, the DCCT (Diabetes Control and Complications Trial) marked a turning point for the therapeutic approach. For the first time, the trial demonstrated that insulin therapy administered at each meal according to blood glucose provided a better glycemic balance than standard twice-daily administration, and optimally prevented development of complications. The biomarker used for glycemic control in this trial was HbA1C.

HbA1c remains the only biomarker, but the goal is to minimize glycemic variability

Fifteen years later, however, the conclusions from DCCT were questioned by another large trial, ACCORD (Action to Control Cardiovascular Risk in Diabetes). This trial was designed to evaluate the clinical benefit provided by an intensive anti-diabetic approach. The trial showed no benefit, and even a 22% increase in mortality in intensive versus standard treatment groups of diabetic patients. This study points out that even though HbA1C remains the only biomarker, it is important to strive for a better glycemic balance, minimizing glycemic variability.

Learning objectives

The objectives of this educational event are to help delegates understand:

1. The burden of illness of hyperkalaemia in patients with chronic kidney disease (CKD)
2. The risk of cardiac abnormalities and mortality that hyperkalaemia gives rise to in patients with CKD, and how these can be managed
3. The potential of current and investigative therapies to maintain normokalaemia in patients with renal disease

Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Faculty</th>
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<tbody>
<tr>
<td>13:30–14:00</td>
<td>Lunch</td>
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<tr>
<td>14:00–14:10</td>
<td>Chair’s Introduction</td>
<td>David Packham (Australia)</td>
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<tr>
<td>14:10–14:30</td>
<td>Hyperkalaemia and Its Role in Cardiac Outcomes in Patients with CKD</td>
<td>Ziad Massy (France)</td>
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<td>14:30–14:50</td>
<td>Is the Way We Manage Hyperkalaemia Evolving?</td>
<td>Alan Jardine (UK)</td>
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<td>14:50–15:00</td>
<td>Panel Q&amp;A / Discussion</td>
<td>All</td>
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Decoding cellular signaling in ADPKD

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease and the fourth most common cause of end-stage renal disease (ESRD). It accounts for up to 10% of prevalent patients on renal replacement therapy (RRT) with estimated related annual healthcare expenditure of 1.6 billion Euros within the European Union (EU). Until recently, ADPKD has been considered a ‘disease without cure’ with no effective treatment to modify the inexorable course to ESRD.[1]

A selective vasopressin receptor-2 antagonist, tolvaptan, has been recently approved for use within the EU to slow the progression of renal disease in patients with evidence of ‘rapid disease progression’.[2] However, tolvaptan is only moderately effective and has significant (aquaretic) and some unpredictable (liver toxicity) side-effects, thus reducing its acceptability and tolerability to many patients in the context of life-long treatment. Therefore, the search for more effective and safer drugs remains a major goal.

A better understanding of the cellular and molecular pathogenesis of ADPKD has given rise to new avenues for drug development. It is well known that the cystic cellular phenotype is characterized by increased cell proliferation, apoptosis, and fluid secretion in addition to changes in cell adhesion and cell polarity. Consequently, the two classical approaches adopted to develop new therapeutics for ADPKD have involved the testing of anti-proliferative and anti-secretion agents in cellular and animal models.[3] The former has benefited from advances in anti-cancer drugs, although unacceptable drug toxicity may limit the benefit-to-risk ratio in ADPKD compared to malignancy.

New targets for personalized and precision medicine approaches to management and treatment

A common signaling intermediate linking both proliferation and fluid secretion is cyclic AMP (cAMP) and approaches to reduce renal cAMP levels have benefited from a strong scientific rationale. Indeed, this is likely to be the major mechanism underlying the beneficial effect of va- sopressin receptor antagonists and somatostatin analogues. Other major signaling pathways that have been linked to ADPKD pathogenesis include EGFR, JAK-STAT, Wnt and Ca²⁺-although clinical testing of these pathways is awaited.

My group has taken a cellular approach to identify the major altered signaling pathways in ADPKD. First, by analyzing the transcriptomes of human cystic and non-cystic kidney epithelia, we identified over 1500 genes that were differentially expressed (over two-fold) in ADPKD cells compared to controls. [4] Using pathway enrichment analysis, at least 30 dysregulated pathways were identified, including the EGF/ErbB pathway.

Of the ErbB members analyzed, ErbB4 (but not other ErbBs) was differentially expressed in diseas e cells. We went on to confirm that ErbB4 overexpression and activation has functional significance in ligand-activated cyst assays and can be detected in human ADPKD kidneys, mouse Pkd1 models and in human urinary exosomes. The latter unexpectedly showed that exosomal ErbB4 outperformed kidney length as a prognostic marker for more rapid eGFR decline (>3 mL/min/1.73 m²) in ROC analysis.

Second, we utilized a focused siRNA screen to analyze components of the JAK-STAT pathway in regulating proliferation in cystic cells.[5] This led us to identify the GH-STAT5 axis as an unrecognized pathway activated in ADPKD models. Future work will focus on strategies to block novel components of these two well-known pathways (EGF/ErbB and JAK-STAT) in addition to strategies to lower cAMP. It is of interest to note that soma tostatin analogues are known to block GH secretion, apart from their effect on cAMP synthesis.

Finally, it is becoming evident that the cystic cellu lar phenotype is much more complex than initially thought, and therefore targeting a single pathway may not be sufficient to inhibit ADPKD throughout life. Emerging features such as altered metabolism, autophagy, inflammation, oxidative stress and epigenetic modification have been reported from preclinical models of disease, although the relative importance of each pathway at different stages of disease and whether they are adaptive or maladaptive, are important issues to resolve. Nonetheless, they open up new avenues for novel drug development and testing beyond the classical approaches. Alongside advances in genotyping and imaging for prognostic risk scoring, the future offers exciting possibilities to develop personalized and precision medicine approaches for the management and treatment of ADPKD patients.

References

Tubular dysfunction: a pathway for AKI

Acute kidney injury (AKI) is characterized by an abrupt reduction in kidney function (i.e. glomerular filtration rate), occurring within a relatively short period. The etiology is most likely multifactorial, but the main focus has historically been directed towards ischemia-reperfusion related mechanisms. Indeed, sufficient blood perfusion to uphold net filtration pressure is a prerequisite to sustain normal glomerular filtration rate, but other parameters also influence filtration across the glomerular membrane. This is supported by recent reports demonstrating normal or near-normal renal perfusion in both experimental models and patients with AKI.

The net filtration pressure across the glomerular membrane is influenced by three seemingly distinct parameters: hydrostatic pressures in the glomerular capillary and in the Bowman’s space, as well as the colloid osmotic difference between the capillary blood and the primary urine. The hydrostatic pressure in the glomerular capillary is the main driving force for glomerular filtration and is autoregulated within the normal blood pressure range. Hydrostatic pressure in the Bowman’s space opposing filtration is almost equal to the hydrostatic free-flow pressure in the early proximal tubule, which is heavily influenced by tubular reabsorption and hydraulic resistance. The colloid osmotic pressure difference across the glomerular membrane is the result of the inability of proteins and blood cells to pass across the glomerular membrane. The resulting higher colloid osmotic pressure in the glomerular capillary opposes filtration.

The reports of normal blood perfusion during acute kidney injury directed our interest towards understanding the role of tubular function in determining glomerular filtration. Since we have a mouse model lacking a functional tubuloglomerular feedback mechanism, we were able to isolate the effects of tubular reabsorption per se as well as indirect effects related to altered feedback signaling.

Increased proximal tubular reabsorption due to increased flux through sodium glucose-linked transporters is a main mechanism for glomerular hyperfiltration in diabetes. Furthermore, reduced proximal tubular reabsorption after inhibition of carbonic anhydrase in the normal healthy kidney significantly reduces the filtration rate. Recent reports have also demonstrated a substantial influence of tight junction properties on proximal tubular reabsorption. Given that proximal tubule reabsorption accounts for about 67% of the total filtered load of electrolytes and volume, any reduction of reabsorbed volume will ultimately result in increased hydraulic resistance as this extra volume flows along the distal parts of the nephron. This will increase the hydrostatic pressure of the proximal tubule and oppose net filtration across the glomerular membrane.

Thus, proximal tubular function will have a profound effect on the glomerular filtration rate and significant proximal tubular dysfunction has the potential to cause acute kidney injury independently of renal blood perfusion. The exact mechanisms for loss of tubular function in acute kidney injury remains to be identified, but could potentially include slipping of sodium pumps, paracellular back leak of electrolytes and water, or mitochondrial dysfunction. However, these mechanisms could potentially be new therapeutic targets to prevent and reduce the severity of acute kidney injury in order to improve the outcome for these patients.

Session 2.1
Actualities and new questions in adult polycystic kidney disease
Tuesday, 08.00 – 09.30, Hall R101 – 102

Session 9.1
Detection and prevention of AKI in patients at risk – state-of-the-art 2017
Tuesday, 08.00 – 09.30, Hall N103 – 104
The Organising Committee/Course Director is responsible for ensuring that all potential conflicts of interest relevant to the event are declared to the audience prior to the CME activities.

In compliance with EBAC guidelines, all speakers/Chairpersons participating in this programme have disclosed or indicated potential conflicts of interest which might cause a bias in the presentations.

**SGLT2 Inhibition: A New Hope for Renal Protection?**

**Learning objectives**

The objectives of this educational event are to help delegates understand:

1. The current epidemiological trends, threats and treatments in patients with chronic kidney disease (CKD)
2. The mode of action, renal safety and renal effects of SGLT2 inhibitors in patients with Type 2 diabetes and healthy individuals
3. The potential roles and mechanisms of SGLT2 inhibitors in CKD

**Agenda**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Faculty</th>
</tr>
</thead>
<tbody>
<tr>
<td>13:30–14:00</td>
<td>Lunch</td>
<td></td>
</tr>
<tr>
<td>14:00–14:10</td>
<td>Chair’s Introduction</td>
<td>Per Henrik Groop (Finland)</td>
</tr>
<tr>
<td>14:10–14:30</td>
<td>SGLT2 Inhibitors: Building a Case for Evidence-based Kidney Protection</td>
<td>Hildo Lambers-Heerspink (Netherlands)</td>
</tr>
<tr>
<td>14:30–14:50</td>
<td>Renal Effects of SGLT2 Inhibitors</td>
<td>Paola Fioletto (Italy)</td>
</tr>
<tr>
<td>14:50–15:00</td>
<td>Panel Q&amp;A / Discussion</td>
<td>All</td>
</tr>
</tbody>
</table>

Monday, 5th June 2017
13:30–15:00
Hall N105–106

**The search for a ‘renal troponin’ continues**

RAYMOND VANHOLDER
Geet Beugem

The last decades have been characterized by an intensive search by the scientific and clinical nephrological communities for appropriate biomarkers of acute kidney injury (AKI). Indeed, serum creatinine, the classical marker, starts to rise only when kidney function has already decreased substantially. In addition, its concentration depends not only on kidney function, but also on many confounders, among which muscle mass and volume status are prone to change during the course of AKI.

Therefore, in analogy with the view of cardiologists when confronted with a suspected myocardial infarction, one may state that the nephrological community is in search of a renal troponin. Although several AKI biomarkers have been identified and some of them have even been commercialized, it remains an open question whether an equivalent of troponin is currently available in acute nephrology.

The history of alternative biomarkers of AKI started in 2005 with the detection of neutrophil gelatinase-associated lipocalin (NGAL). A result of targeted proteomic research, this marker allowed a clear distinction between subsequent AKI and no AKI in children undergoing cardiopulmonary bypass. This was, however, a clear-cut situation where individuals with few if any comorbidities (children) underwent a potentially kidney-damaging condition at a well-defined moment.

Building further on the example of NGAL, which is the most extensively studied of the potential biomarkers, later analyses often showed less reassuring results in less well defined conditions prone to AKI development such as sepsis. These pointed to the presence of overlap between individual values in chronic kidney disease (CKD), pre-renal (transient) AKI and intrinsic AKI – the three conditions between which AKI biomarkers are supposed to allow distinction and offer therapeutic guidance. In addition, it soon became obvious that, like serum creatinine, NGAL could also be raised in conditions other than AKI – e.g. in sepsis with unaffected kidney function – and that it is as much a marker of severe disease and inflammation as of AKI. Finally, it still has not been clarified when exactly during the course of a condition causing AKI these biomarkers should be determined. This might lead to multiple measurements of a test that is more expensive than creatinine determination, without certainty about the value that would be the most appropriate diagnostically. In some of these studies the added value of markers over clinical judgment is minimal. Similar conclusions can be drawn about single markers other than NGAL.

More recently, the cell cycle markers have been identified and validated. The combination of tissue inhibitor of metalloproteinases-2 (TIMP2) and insulin-like growth factor-binding protein-7 (IGFBP7) has drawn special attention by more promising receiver operating characteristic (ROC) curves than NGAL and the other biomarkers of the same generation. Unfortunately, subsequent studies on TIMP2/IGFBP suffered from similar pitfalls to the other biomarkers: i.e. a fair discrimination in clear-cut situations (AKI in children, cardiac surgery) or when the cut-off values remained high enough (at the expense of sensitivity), but more overlap between AKI and no AKI when studied in more complex conditions. For these reasons, cell cycle markers need further study before their exact place in the diagnosis of AKI can be defined.

Should we then entirely discard the concept of AKI biomarkers? The answer is no. First of all, they taught us a lot on the pathophysiology of AKI. Second, they are useful in well defined situations such as in children or after cardiovacular surgery, and possibly for diagnosing delayed graft function after kidney transplantation. Third, biomarkers may be helpful in follow-up of interventional trials of nephroprotective measures, where they could offer a more sensitive indication of kidney damage, or may even at the start of development of novel nephroprotective therapies. Finally, they may also detect nephrotoxicity more quickly than the classic detection methods.

In conclusion, the currently available biomarkers for AKI cannot offer the same sensitivity and specificity as troponin does in myocardial infarction. Probably AKI is more heterogeneous and complex than myocardial infarction, and therefore the condition may need more complex multi- marker or specific markers for specific types or phases of the disease. Current AKI biomarkers discriminate statistically between the three key conditions they would need to distinguish (i.e. pre-renal AKI, CKD and intrinsic AKI) in large groups, but not always and consistently in individual cases due to substantial overlap. The picture is further blurred by interference of inflammatory conditions, including sepsis and severity of disease. Before AKI biomarkers can grow into clinical adulthood, they need to demonstrate a more refined capacity to discriminate that is successfully corroborated by clinical and health economic data based on randomized interventional trials.
Cardiac involvement in kidney disease has been recognized for decades. Originally ascribed mainly to volume overload and hypertension, it has become clear that many more factors are involved, including the sympathetic nervous system, renin-angiotensin system, and metabolic or endocrine factors. Among the latter category both fibroblast growth factor 23 (FGF23) and α-Klotho are in the spotlight, and recent new data corroborate their key roles in the development of uremic cardiomyopathy. Although in the general population, where concentrations of FGF23 are obviously relative-normal, the association between FGF23 and cardiovascular disease is still debated (Framingham), there is an exceptional consistency for this finding in patients with CKD. All-cause and cardiovascular mortality, cardiovascular events, especially atrial fibrillation, all occur more frequently if FGF23 concentrations are higher in these patients. To date, proof of a causal role for FGF23 is still lacking, but both additional epidemiological data and mechanistic studies do further support that assumption.

A post hoc analysis of the EVOLVE trial showed that a decline of FGF23 over time, induced by the use of cinacalcet, was associated with an improvement of the composite clinical outcome. The previously shown direct induction of left-ventricular hypertrophy (LVH) by FGF23 is now pinpointed as being mediated by signal transduction through the FGF receptor type 4. Although α-Klotho is not required for this signaling itself, it can apparently still be protective against FGF23-driven cardio toxicity as exemplified for the development of cardiac fibrosis (Figure). Therefore, high concentrations of FGF23 in a setting of α-Klotho deficiency—the typical situation for CKD—induces uremic cardiomyopathy. An alarming recent finding is that heart failure itself induces FGF23. Then a vicious circle operates, with the failing heart signaling its own death warrant and closing a feed-forward loop.

Klotho and FGF23 in the spotlight

(FGF23) and α-Klotho are in the spotlight, and recent new data corroborate their key roles in the development of uremic cardiomyopathy. Research in animal models of chronic kidney disease suggests that Klotho deficiency increases the risk of cardiovascular disease and death. FGF23, a protease secreted by osteocytes, is involved in phosphate and vitamin D metabolism and is regulated by Klotho. In patients with chronic kidney disease (CKD), cardiovascular (CV) complications and mortality occur several times more frequently than in appropriately selected subjects with normal kidney function. In patients with end stage kidney disease (ESKD), CV complications are most often present as uremic cardiomyopathy with left ventricular (LV) hypertrophy, often accompanied by coronary artery disease, which predisposes to the development of congestive heart failure (CHF). Besides hyperparathyroidism, pathogenesis of uremic cardiomyopathy includes interstitial expansion with fibrosis, and reduced capillary density, abnormalities that contribute to the increased susceptibility to ischemic injury with a high rate of maligl arrhythmia. These features can be reproduced in experimental models of chronic uremia in rats. Uremia may deteriorate cardiac function directly, impairing myocyte relaxation and inducing fibrogenesis. Hormonal abnormalities may additionally contribute to the initiation and maintenance of uremic cardiomyopathy in ESKD patients. Discoveries of such new mechanisms of uremic cardiomyopathy are needed in order to identify novel therapeutic targets for reducing the burden of cardiovascular disease in these patients. The following endocrine mechanisms participating in uremic cardiomyopathy are currently recognized:

- inappropriate activation of the sympathetic nervous system
- inappropriate activity of the renin-angiotensin-aldosterone system (RAAS)
- elevated plasma vasopressin levels (AVP)
- secondary hyperparathyroidism
- elevated local and circulating levels of fibroblast growth factor 23 (FGF23)
- hyperinsulinemia and insulin resistance
- elevated serum concentration of endogenous cardiac troponins (mainly marinobufagenin-MBF)
- elevated plasma natriuretic hormones—mainly atrial (ANP) or brain (BNP) natriuretic peptides
- dysbalance of adipokine secretion (leptin, adiponectin, apelin, etc.)
- dysbalance of endothelin/nitric oxide secretion
- inappropriately low serum vitamin D (25-OH-D) concentration
- deficiency of circulating soluble (s)Klotho and tissue Klotho levels
- inappropriately low serum erythropoietin (EPO) concentration
- inappropriately low serum growth hormone concentration (IGH)
- inappropriately low serum renin concentration

Potential mechanisms combined with the endocrine abnormalities in the pathogenesis of cardiomyopathy in CKD patients are summarized in Fig. 1.

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<th>Cardiorenal related factors</th>
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<td>Sympathetic tone activation</td>
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<td>Endothelin</td>
<td>NO inhibition</td>
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<td>Renalase</td>
<td>NO activation</td>
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<tr>
<td>Nitric oxide</td>
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</tbody>
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Figure 1: Modification from: Kazuhiro T and Masahiro E., Curr. Opin. Nephrol. Hypertens., 2015, 24, 154–162

As already mentioned, not all of these therapeutic options have been tested in prospective randomized clinical trials. A better understanding of the most relevant pathophysiological pathways for uremic cardiomyopathy may lead to better therapeutic interventions against cardiovascular CV disease in patients with ESKD. However, more studies are still needed in order to determine the beneficial effects of the aforementioned therapies in the treatment of cardiomyopathy in these patients.
The relationship between cardiovascular (CV), renal and metabolic disease is well known. [1] Deeper understanding of the pathophysiological interactions among these diseases has underscored the potential dangers of high serum levels of the potassium electrolyte, known as hyperkalaemia. [2]

Hyperkalaemia affects up to 50 percent of chronic kidney disease (CKD) patients and approximately 20 percent of congestive heart failure patients taking mineralocorticoid receptor antagonists. [3, 4] Potassium homeostasis is critical for physiological activity of excitable cells such as cardiac muscle cells, skeletal muscle cells and neurons. [2] Severe hyperkalaemia can, therefore, cause cardiac arrhythmias and cardiac arrest, as well as skeletal muscle weakness and paralysis. [5] Unmanaged, acute hyperkalaemia therefore constitutes a medical emergency and may even lead to death. [6]

Despite these severe consequences, hyperkalaemia is an under-recognised condition. It can remain asymptomatic until severe damage occurs, and is difficult to manage. [2] Hyperkalaemia often requires strict diet modifications that conflict with guidance for pre-existing conditions. [2] It also often requires changes to baseline renin-angiotensin aldosterone system inhibitor (RAAS) therapy, potentially compromising prescribed therapy. [3] In order to improve the patient’s quality of life and reduce related mortality, the management of hyperkalaemia should be prioritised.

At congresses like ERA-EDTA 2017, scientific experts will gather to understand the latest data and science, which inform how we manage patients suffering from chronic disease and its complex comorbidities. AstraZeneca will be presenting 13 real-world evidence studies at ERA-EDTA – two of which are being presented as oral sessions and evaluate patients’ actual experiences living with CKD and hyperkalaemia, among other conditions.

- The first study (M0066) reports on a prospective cohort study based on comprehensive hospital contact, medication and laboratory databases for 145,352 incident CKD patients in northern Denmark during 2000–2002. [7] Outcome rates were controlled for differences in comorbidity and CKD severity using Cox regression. [7] During a four-year follow-up period, 23 percent of CKD patients experienced a hyperkalaemic event. [7] Among CKD patients, those with chronic heart failure or those treated with the potassium-sparing diuretic spironolactone had almost three times the risk for hyperkalaemia, as compared to patients without these factors. [7] Hyperkalaemia increased the six-month mortality risk by five-fold compared to CKD patients without hyperkalaemia. [7] These findings illustrate the complexities involved in the pharmacologic management of cardio-renal care.

- The second study (M0067) examined the association between serum potassium levels and key clinical outcomes using retrospective, observational data from a cohort of 144,388 UK patients with CKD. [8] Key clinical outcomes observed include mortality and major adverse CV events (MACE) such as cardiac arrhythmia, myocardial infarction, stroke and heart failure exacerbation. [8] Incidence rate ratios for outcomes were adjusted for age, sex, diabetes, cerebrovascular accident and use of certain medications. These data showed a strong association between abnormal serum potassium levels and mortality and MACE, with higher adjusted incidence rate ratios at hyperkalaemic (≥ 5.0 mEq/L) and hypokalaemic (< 3.5 mEq/L) serum potassium levels. [8] A similar but stronger trend was observed between serum potassium levels and mortality. [8] Findings are consistent with previously reported US-based real-world data, further emphasising the increased risk of mortality and MACE among CKD patients with hyperkalaemia.

These real-world evidence data provide further insight into the risks associated with hyperkalaemia and reinforce the need to act promptly when hyperkalaemia occurs. Specifically, we see the need for swift, sustained options to treat hyperkalaemia safely at point of care and at any level. It is imperative that our industry moves towards continuous control in both acute and chronic hyperkalaemia management, especially among high-risk populations like those with renal disease.

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References


Figure 1: The interaction between high FGF23 and low α-klotho in the development of cardiac fibrosis. Especially when α-klotho concentrations are low. Modified from Hu et al. [1]
Physical exercise programs in CKD: what is the evidence?

Coherent evidence exists that physical activity and cardiovascular fitness decline early in CKD. Physical inactivity is a progressive phenomenon that parallels the deterioration of renal function towards kidney failure. Physical reconditioning, as well as the multiple metabolic alterations triggered by the presence of renal dysfunction, reduce muscle mass and function, particularly in advanced CKD stages.

Physical inactivity is associated with low quality of life (QoL), and with major clinical outcomes including death and cardiovascular events in CKD. Together with protein-energy wasting, a sedentary lifestyle is now regarded as a potentially modifiable risk factor and as an important target to improve QoL and clinical outcomes in these patients. Evidence is emerging that physical rehabilitation programs may benefit CKD patients, but the vast majority of studies that investigated this problem are of small dimension and suboptimal quality. Of note, some data suggest that maintenance of muscle mass may retard CKD progression, but again we still lack a proper trial testing these interesting hypothesis-generating data. There is still a lack of studies defining the type of physical exercise that better suits CKD patients and to date we have no information about the required frequency and intensity of physical activity in these patients. Recent secondary, pre-specified analyses performed within the framework of a randomized clinical trial in stage 5D CKD patients maintained on chronic dialysis show that a simple, home-based walking exercise program profiled to the individual's performance not only increases walking capacity but also reduces the risk of hospitalization in these patients.

Overall, regular physical activity has the potential to improve quality of life and clinical outcomes at all CKD stages in patients with chronic kidney disease (CKD), but definitive research demonstrating that interventions aiming at improving physical performance may also improve clinical outcomes in these patients is still lacking. Clinical trials testing these interventions should be considered a priority by clinical investigators interested in outcome research in CKD.

References

Session 4.6
Physical exercise and lifestyle management in chronic kidney disease
Tuesday, 08.00 – 09.30, Sala Retiro

Let's enjoy life together!

In his book “Understanding Human Nature”, published in 1927, Adler included one chapter about “The human lifestyle”. In that chapter he describes and defines lifestyle as a childhood-rooted, unique, unconscious, and repetitive way of relating to the individual’s main tasks of living, in which he numbered friendship, love, and work. His argument was that, since these behavioral structures were engramed in childhood, they are almost impossible to change. In fact, this is what we observe: people do not change their lifestyle even after catastrophic events such as the diagnosis of lung cancer in smokers.

References

Digital applications have an increasing role in CKD and other chronic diseases

Can benefit from online screening and tailored self-management treatments. eHealth is also an important instrument to empower patients and can contribute to shared decision-making. Moreover, digital solutions are increasingly used for the prevention of chronic somatic and mental conditions, such as heart diseases and depression.

The main aim of eHealth and self-management initiatives is to optimize healthcare for a wide variety of patient groups by developing, evaluating, and implementing online screening instruments and self-management interventions that can be tailored to individual needs. The initiatives encompass a broad variety of projects that develop and test the effectiveness of digital screening instruments to select subjects at risk and offer them tailored interventions (e.g. online self-management interventions for patients at risk of ad-

Digital applications have an increasing role in CKD and other chronic diseases

Session 4.6
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Tuesday, 08.00 – 09.30, Sala Retiro

Modifiable lifestyle factors in high-risk individuals with CKD

Recent large randomized controlled trials with exceptional data quality and thorough lifestyle questionnaires were used to identify risk factors for and identify associations with the incidence and progression of chronic kidney disease (CKD). The ONTARGET and ORIGIN studies followed more than 40,000 patients for over five years. We were primarily interested in studying the associations of potentially modifiable risk factors, such as diet, alcohol intake, smoking, exercise, and social factors, with CKD outcomes. Not unexpectedly, but statistically sound, we could show that a healthy diet was associated with a lower incidence and progression of CKD. Accordingly, mild alcohol intake, moderate physical activity and a larger physical social network were associated with better outcomes. Interestingly, financial worries played a minor role.

In summary, apart from the intuitive lifestyle changes towards a healthier diet and smoking cessation, humans as social creatures obviously benefit from maintaining functioning physical social networks – i.e. let’s enjoy life together!

References

Let’s go online for eHealth and self-management

Healthcare is increasingly characterized by digital eHealth applications such as apps, serious games, or e-coaching, for both the prevention and treatment of somatic and mental conditions.

Digital applications have an increasing role in CKD and other chronic diseases

including chronic kidney diseases (CKD). For example, CKD can not only result in physical complaints such as pain, itch and fatigue, but also negative mood, limitations in daily activities, and impairments in social relationships. CKD and other patients with chronic somatic conditions
“Mens sana in corpore sano.” The Roman poet Ju-venal knew 2000 years ago that physical health goes hand in hand with mental health. However, scientific evidence that physical exercise benefits human health is much more recent, being first documented in the 20th century in a cohort of Harvard University alumni enrolled between 1916 and 1950. In that large cohort of men, physical activity was shown to reduce the risk of coronary artery disease. In other words, the higher the level of physical activity, the lower the risk of coronary events in those men.

Physical activity reduces cardiovascular risk, not only in the general population, but also in high-risk patients such as those with heart failure, in whom the beneficial effects of physical activity on risk of death and hospitalization have been convincingly documented. As far as dialysis patients are concerned, the effects of some kinds of physical activity have been investigated only in hemodialysis patients—who, by definition, are at high risk—in small, single-center studies involving supervised exercise during the dialysis session or in hospital. There is no question that the fact that all these studies were performed during dialysis sessions represents a strong limitation on patient empowerment. Indeed, home-based, extra-dialysis physical exercise programs would considerably enhance feasibility and adherence.

The aim of the randomized, controlled EXCITE (EXerCise Introduction To Enhance performance in dialysis) clinical trial [1] was therefore to test the effects on physical performance in dialysis patients of a low-intensity, easy-to-implement, home-exercise program. This multicenter study was undertaken in 9 dialysis centers in Italy and the primary analyses showed a significant improvement in their performance either for the Six Minute Walking Test or the Sit-to-stand-to-sit Test, while no changes were recorded in the control group. Not surprisingly, changes in cognitive function and in quality of social interaction items of the KDQOL-SF were significantly more favorable in the exercise group than in the control arm.

Results of the EXCITE trial

The EXCITE trial included a post-trial observation period (36 months), during which data on death, cardiovascular events and hospitalizations were collected. During follow-up, 134 events were recorded. In 126 cases, hospitalization was the first event, followed by death in 36 cases, whereas in 8 cases patients died without hospitalization. Statistical analyses showed that during the trial (follow-up 6 months: short-term risk) the risk of hospitalization was significantly reduced in the exercise arm compared to the control arm. The same analysis extended to the post-trial observation period (36 months: long-term risk) confirmed the risk reduction (-29 %) for hospitalization.

Furthermore, in analyses taking into account adherence (compliance) to the waking exercise program, the subgroup with high adherence exhibited the lowest risk of hospitalization compared to the control arm and to patients with low adherence. Separate analysis for mortality showed no significant difference between the groups.

In conclusion, these results in a fairly large cohort of dialysis patients indicate that a simple, person-alized, home-based, low-intensity exercise program managed by dialysis staff improves physical performance and quality of life, and reduces short- and long-term risk of hospitalization in patients who maintain a high adherence. These findings are the starting point for the design of clinical trials based on clinical endpoints to test the effect of physical rehabilitation programs in this high-risk population.

References

1. ClinicalTrials.gov NCT01255969

Session 4.6
Physical exercise and lifestyle management in chronic kidney disease
Tuesday, 08.00 – 09.30, Sala Retiro
Although the data reported above, particularly with respect to the predictive power for cardiovascular events [8,9]. In a larger study comprising 444 well-characterized CKD stage 2–4 patients, we failed to observe a strong relationship between sFGF23 and soluble Klotho levels in CKD patients, but yielded conflicting results with respect to the protective power for cardiovascular events [8,9]. In addition, we did not find any correlation between sKlotho andcardiovascular end-points. Instead, FGF-23 levels turned out to be the best parameter of calcium-phosphate metabolism for predicting adverse outcome. The strongest evidence that CKD is a state of Klotho deficiency comes from a post-mortem study by Leifheit-Nestler et al. [10], who found a significant association between LHV and enhanced expression levels of FGF-23, FGF23 and calcineurin activation of NFAT, and reduced levels of soluble Klotho in the myocardium of patients with advanced CKD. This point is pertinent if one considers the use of recombinant soluble Klotho protein for the prevention of cardiomyopathy associated with advanced CKD.

References
Explaining genetic abnormalities in C3 glomerulopathy

C3 glomerulopathy (C3G) is a heterogeneous group of very rare kidney diseases driven by uncontrolled activation of the complement cascade that leads to C3 deposition within the glomerulus. No specific treatment is currently available for C3G. Two major subtypes of disease are recognized that are identified by distinctive electron microscopic findings on renal biopsy: in dense deposit disease (DDD) there is an intense deposition within the glomerular basement membrane (GBM), whereas in C3 glomerulonephritis (C3GN) the deposits are much more diffused and extend to the mesangium and sub-endothelial or sub-epithelial locations. In most DDD patients, complement dysregulation results in massive activation and consumption of C3, whereas in C3GN C3 levels are often at the lower level of the normal range.[1]

Genetic and/or acquired defects drive the alternative pathway dysregulation that characterizes C3G. The genetic component is large, and the AP C3 convertase by FH and CR1. In this respect they resemble FH functional deficiencies. Interestingly, however, there are subtle functional differences between these two C3G-associated C3 variants that result in distinct fluid phase C3 consumption. C3-923ΔDG completely consumes C3, but C3-I756T does not, which likely explains the distinct fluid phase and almost a complete penetration of the disease.

The FH proteins modulate the complement regulatory activities of FH on self and non-self surfaces. These proteins lack the complement regulatory domains of FH, but have conserved the FH surface recognition domains, which confer upon them the capacity to compete the binding of FH to complement-activating surfaces. This FH antagonistic function of the FHRs is termed complement de-regulation.[2] It is postulated that the abnormal FHR-1, -2 and -5 proteins associated with C3G compete in excess the regulatory activity of FH on the GBM with pathological consequences.

How and where this competition takes place is only beginning to be understood, but it is thought that the carbohydrate composition of the GBM, immunostaining data illustrate an intense glomerular staining for FHR proteins found in carriers of these genetic alterations (Figure 2). Also supporting this hypothesis is the protective role from C3G conferred by the DelCFHR3-CFHR1 polymorphisms. Whether development of C3G in conditions in which levels of the FHRs are abnormally elevated or in carriers of gain-of-function FHR variants is triggered by otherwise ‘normal’ complement deposition and/or modifications of the carbohydrate content of the GBM, is presently unknown.

As a whole the data generated in the functional and molecular characterization of these C3G-associated variants illustrate the heterogeneity of the pathogenic mechanisms underlying C3G, which may help, for example, to provide a better distinction between different C3G subtypes, to inform prognosis or recommend treatment. Additional data are, however, needed to have a complete understanding of the genetic drivers in C3G and their pathogenic implications. This can only be obtained through the genetic screening of increasing numbers of C3G cases and through studies on the effect of disease-associated variants on protein function.

References

Figure 1: The percentages of individuals carrying genetic variants in the different C3G candidate genes in the Spanish C3G Registry (n=156) and in those who are C3Ref negative and C3Ref positive.

Figure 2: The FH/FH-1 immunoperoxidase staining of a kidney biopsy from a C3GN patient carrying a FH-1 protein with a duplicated oligomerization domain. Notice the localization of the FH-1 protein along the GBM.
It has been estimated that the global burden of diabetes mellitus (DM) will affect more than 435 million people in the year 2015, with a significant growth across the five continents, from 81% in Latin America to 255% in Asia, according to the International Diabetes Federation.

Despite the growing DM population, trends in age-standardized rates of diabetes-related complications, such as acute myocardial infarction, stroke or amputations, seem to have decreased in recent years, but without reducing the incidence of advanced chronic kidney disease (CKD) requiring renal replacement therapy (RRT). Diabetic kidney disease (DKD) continues to be the leading cause of end-stage renal disease (ESRD), explaining why each year 24% – 55% of patients with ESRD need to start RRT. The natural history is different in type 1 DM and in type 2 DM, but early detection of both DM and DKD is crucial to reduce complications, morbidity and mortality, as well as the social and economic impact of the DM burden in this population.

The classical pattern of DKD includes the presence of microalbuminuria and progression to proteinuria. However, in the last few years a probable non-proteinuric phenotype of DM patient has been described, and many patients show progressively decreasing glomerular filtration rate (GFR) without developing proteinuria. In some instances, an atypical evolution showing urinary sediment abnormalities, accelerated proteinuria or the absence of retinopathy requires a renal biopsy to rule out the presence of non-diabetic renal disease.

Depending on the estimated progression of GFR decline, the degree of proteinuria, comorbidities, and the presence or absence of alarm signs, consensus documents and clinical practice guidelines recommend referral of the DM patient to Nephrology when estimated GFR (eGFR) is < 30 mL/min/1.73 m² or when proteinuria is > 300 mg/g creatinine. Other remission criteria should include acute deterioration of renal function (> 25% of baseline), renal progression (eGFR > 5 mL/min/1.73 m²/year), refractory HT, potassium > 5.5 or < 3.5 mEq/L, renal anemia – Hb < 10.5 g/dL, with CKD and corrected ferropenia (IST > 20% and ferritin > 100 ng/mL, or mmol/L) – alarm signs or suspicion of non-diabetic nephropathy.

There is the question of whether global care of the DM patient is adequate in Nephrology departments. We will provide data from the MERENA and PECERA studies to consider if integrated care and management of the patient with DKD are optimal. A more controversial, key point concerns the management of hyperglycemia in the DM patient with renal insufficiency. We will also present some data from the EXPLORE study about the management of type 2 DM patient in primary care settings and also in Nephrology services in Spain.

In the last part of the presentation we will discuss some aspects of the renoprotective effects of the new hypoglycemic drugs like DPP4 inhibitors, GLP1 agonists and SGLT2 inhibitors when prescribed to DM patients with GFR < 60 mL/min/1.73 m².

Finally, we should remember that good glycemic control retards the initiation of microalbuminuria and progression to overt proteinuria in DM patients (Evidence 1A). Some studies have demonstrated that optimal glycemic control retards the progression of renal damage in DM patients (Evidence 1B), but others have been unable to provide this evidence. It seems clear that optimal glycemic control is necessary to minimize vascular damage in DM patients, especially when renal damage appears and also to reduce comorbidities and mortality (Evidence 1A). Tight metabolic control is only recommended in DM patients with DRD when the episodes of hyperglycemia are minimized (Evidence 1B).

To conclude, we recommend taking into account all these considerations when referring the patient with DM and DKD to nephrologists in the early stages of their renal disease.

References

Session 4.3
Biomarkers in chronic kidney disease
Tuesday, 10.45 – 12.15, Hall 10A

The advantages of early referral are clear
Advances in technical and biotechnological tools and methods enable measurement of the real levels of both a specific immunosuppressive drug and its toxic metabolites. As a natural consequence of phases I and II of drug biodegradation, drug metabolites become detectable in the plasma or tissues. Some of these metabolites are toxic, but our knowledge of this subject is very limited. Older enzyme immunoassay (EIA)-based methods yield fluctuating results that are often about 30% higher than actual levels. In contrast, widely used modern liquid chromatography/mass spectrometry (LC/MS) methods obtain accurate drug level measurements. However, improved data acquired using modern methods are often not applied in clinical settings. In the present study, LC/MS methodology was used to measure levels of a drug and its metabolites in whole-blood samples collected from a cohort of nearly 300 patients after kidney transplantation. Our preliminary data clearly indicate the potential usefulness of the metabolites trihydroxy-cyclosporin (TriH-CsA) and 15-O-demethyl-tacrolimus (MIII-Tac) for drug toxicity monitoring. Our preliminary results warrant the initiation of multicenter studies of serum drug levels and metabolite pharmacokinetics. Future studies should include the analysis of large data sets, comparisons among patients, and graft follow-ups. ERA-EDTA could be the leading group to undertake these projects. The results of such work could serve as the basis for new guidelines for immunosuppression in kidney transplantation.

What’s on in Madrid?

**Vladimir and Vovka Ashkenazi**

One of the most acclaimed conductors of today, Vladimir Ashkenazi, is coming to the city with his son Vovka to perform a piano recital as part of the Great Performers Programme organised by the Scherzo Foundation, featuring a selection of great romantic pieces that will fully engage the Russian musicians.

**National Music Auditorium**

Calle Príncipe de Vergara, 146 28002

Today, 7.30 pm

**Café de Chinitas**

This restaurant-flamenco venue first opened its doors in 1970, in a lovely 18th Century palace, with decor inspired by Federico García Lorca and the world of bullfighting together with Manila shawls. Lose yourself in the magical charm of flamenco and Spanish gastronomy!

Calle Torija, 7 28013

Today, 8.00 pm – 1.00 am

**Ramon Casas: The Desired Modernity**

Celebrating the 150th anniversary of the birth of Ramon Casas, this exhibition shows more than 200 of his paintings and prints, which played an active role in the construction of the concept of modern art.

**CaixaForum Madrid**

Today, 10.00 am – 8.00 pm

**The Prado Museum**

The Prado Museum is the crown jewel of one of the capital’s most visited tourist itineraries: the Paseo del Arte (Art Walk). Its collection comprises 8,600 paintings and over 700 sculptures, so we recommend you decide what you want to see before stepping into the museum.

Today, 10.00 am – 8.00 pm

**Impressions of Day 2**

**Helpful or dispensable?**

Leszek Paczek

Leading European Nephrology

Imprint

ERA-EDTA Operative Headquarters
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43123 Parma, Italy

Editor-in-chief
Bettina Albers, PhD

ERA-EDTA Press Office

**Session 46**

Immunosuppression after renal transplantation – less, more or appropriate?

Monday, 17.00 – 16.45, Hall N101 – 102
What’s on in Madrid?

Vladímir and Vovka Áshkenazi

One of the most acclaimed conductors of today, Vladímir Áshkenazi, is coming to the city with his son Vovka to perform a piano recital as part of the Great Performers Programme organised by the Scherzo Foundation, featuring a selection of great romantic pieces that will fully engage the Russian musicians.

National Music Auditorium
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Today, 7.30 pm

Café de Chinitas
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