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EMJ Nephrology

Review of ERA Congress 2022

Editor's Pick

The Renal Effects of SGLT2 Inhibitors

Interviews

Ingeborg Bajema and Edwina Brown provide insights into ERA 2022, while John Sperati and Vivek Bhalla share their experiences from their work in nephrology

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Aims and Scope

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Front cover and contents photograph: Paris, France, home of the **ERA 2022**. **© Tomas Marek** / stock.adobe.com

EMJ Welcome letter

Koutsouki

Evgenia Koutsouki, PhD.
Editor

Dear Readers,

I would like to welcome you to the 2022 issue of *EMJ Nephrology*, bringing you content from the 59th European Renal Association (ERA) Congress in Paris, France. Our team had the great privilege of attending the congress in person and we are delighted to share some of the highlights.

With the overarching themes of the congress being innovation, prevention, and preparedness, the welcome lecture focused on equity in kidney health and explored themes of health inequality across the world. Exciting results of late-breaking clinical trials were also presented, which can be found in our congress highlights section.

On par with the congress theme, this issue features an article on chronic kidney disease in conflict zones and the quality of healthcare in Africa, highlighting the challenges around the rising prevalence of non-communicable diseases in low-resource settings. Other articles include a review on the pathophysiology of diabetic kidney disease and a research article on COVID-19-associated nephropathy.

I am certain that the our new look has not gone unnoticed. This bolder, more dynamic visual identity better reflects the EMJ purpose of elevating the quality of healthcare globally, by supporting all healthcare professionals with free and easy access to independent education and lifelong learning opportunities. We are very excited for this new identity to make its debut in *EMJ Nephrology*.

I would like to close by thanking our Editorial Board, authors, and peer reviewers, who have helped bring together this fantastic selection of content and I hope that you enjoy reading through the issue.

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Foreword

Dear Readers,

I would like to thank all of the authors, peer reviewers, and Editorial Board members who have contributed to this fantastic issue of *EMJ Nephrology*. Their continued commitment and efforts have made the publication of the most up-to-date research in this journal possible.

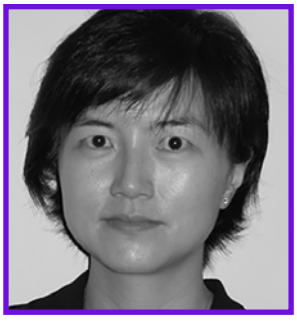
This year's issue contains a selection of original research articles, reviews, and features, alongside a comprehensive review of the 59th Annual European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) 2022 Congress. The articles featured cover timely topics, including COVID-19-associated nephropathy and the pathophysiology of diabetic kidney disease.

Our Editor's Pick for this issue is a highly relevant review exploring the emerging use of sodium-glucose co-transporter-2 (SGLT2) inhibitors in renal healthcare. Sawaf et al. provide an in-depth analysis of the effects of this treatment on different types of kidney disease. Originally used for the management of diabetes, SGLT2 inhibitors are now evolving as key treatment options for both diabetic and non-diabetic kidney disease, and heart failure with preserved or reduced ejection fraction following their recent U.S. Food and Drug Administration (FDA) approval.

A fascinating research article by Uduagbamen et al. delves into the use of low-dose dopamine in the treatment of intradialysis hypotension. Conducted in Nigeria, this retrospective cohort study drew interesting conclusions on the positive effects of this treatment on adverse dialysis effects and termination. Featured alongside this is a topical article covering COVID-19-associated nephropathy as an emerging clinical entity, as well as comprehensive review of SGLT2 inhibitor studies, which provides an overview of upcoming trials focusing on patients with declining glomerular filtration rates.

For those who could not attend, our independent review of the ERA-EDTA 2022 Congress is not to be missed. This featured exciting abstracts written by the presenters themselves

Finally, I hope that you enjoy this issue of *EMJ Nephrology*, and thank you for your continued support.



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ERA 2022

Review of the European Renal Association (ERA) Congress, Paris & Virtual, 19th–22nd May 2022

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THIS YEAR'S 59th European Renal Association (ERA) Congress invited over 1,000 colleagues to a hybrid event in Paris, France, for the first time since the COVID-19 pandemic. Paris has been home to many incredible innovators and has given the world many gems, from the invention of the stethoscope to the science of chemistry. ERA is the largest nephrology congress in Europe, detailing key learning points, late-breaking abstracts, and the latest innovations in the clinical field.

The opening ceremony took us back to the very start of the COVID-19 pandemic in December 2019. Monica Fontana, Executive Director, ERA, Italy, described how the community did not have any idea of how to treat patients with COVID-19 and kidney disease: "We are learning much more every day." The hybrid format of this year's congress enabled healthcare professionals around the world to be educated in the latest updates in nephrology.

This year's congress received an impressive 1,372 abstract submissions from colleagues across 76 countries, an increase from last year's submissions. Most of the abstracts came from professionals in clinical nephrology, dialysis epidemiology, and renal transplantation. Interestingly, most abstracts came from physicians in Spain, Italy, and France. Sessions included diagnostic tools for acute kidney infection, risk factors in chronic kidney disease, and much more.

Additional content and activities during this hybrid event included late-breaking clinical trial (LBCT) summaries, educational activities, and innovative network opportunities. ERA received over 30 LBCT summaries and the committee carefully selected six of the best submissions for the LBCT session. The clinical trials discussed in the summaries took place all over Europe, notably from Germany, Netherlands, Switzerland, France, and the United Kingdom. Topics covered bio-impedance spectroscopy to preserve residual kidney function in incident haemodialysis patients, and the effects of aspirin in primary prevention of cardiovascular disease in people with chronic kidney disease.

During the welcome ceremony, Annette Bruchfeld, Chair of the Scientific Committee, ERA, Stockholm, Sweden, shared the motto of the congress: innovation, prevention, and preparedness. COVID-19 has resulted in nephrologists and other allied healthcare professionals to adapt and think differently. Innovation, prevention, and preparedness were the chosen values, due to their importance during these trying times. Nephrology needs to constantly innovate; new screening techniques could prevent further illness, and preparedness for the future is

important in case of another pandemic or other health crises.

Bruchfeld and other committee members aimed to deliver the best programme by sharing the most important sessions in nephrology. She also thoughtfully considered factors such as gender balance, and this was reflected in the congress itinerary in which half of the sessions were presented by females. The congress kicked off with a welcome lecture by Valerie Luyckx, on "equity, sustainability, and ethics in kidney health."

Finally, ERA awards were given out to outstanding nephrologists in the field. Corinne Antignac, Laboratory of Hereditary Kidney Diseases, Paris Descartes-Sorbonne Paris Cité University, France, received the ERA Award for Outstanding Basic Science Contributions to Nephrology; Ziad Massy, Division of Nephrology, Ambroise Paré University Hospital, Paris, France, received the ERA award for Outstanding Clinical Contributions to Nephrology; and Andreas Linkermann, Division of Nephrology, Carl Gustav Carus University Hospital at the Technical University Dresden, Germany, was awarded the ERA Award for Research Excellence in Nephrology.

A new change this year to the ERA awards was that the Young Investigators Awards were split into three separate awards. These were awarded to Jennifer Lees, Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, UK; Turgay Saritas, Department of Nephrology and Clinical Immunology, RWTH Aachen University, Germany; and Francesco Trepiccione, Department of Internal Medicine, Chair of Nephrology, Faculty of Medicine, Second University of Napoli, Italy.

To those who missed this year's ERA congress, our eJournal covers the key stories, abstract summaries, and interviews in this year's EMJ Nephrology journal, alongside peer-reviewed articles from global pioneering researchers.

Next year is a big year for ERA as they celebrate a momentous milestone of 60 years. We look forward to attending next year's congress in Milan. However, for now, please enjoy our highlights and reviews of this year's congress.

Aspirin and Primary Prevention of Cardiovascular Disease in Chronic Kidney Disease

DURING the 59th ERA Congress, Johannes Mann, Professor of Medicine, University of Erlangen-Nuremberg, Germany, discussed the effects of aspirin in the primary prevention of cardiovascular disease in people with chronic kidney disease (CKD).

Results were derived from a subgroup analysis of the TIPS-3 trial. CKD was defined as an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m2. Participants were randomised to a polypill, which Mann explained was "one pill containing atenolol, ramipril, thiazide, and simvastatin," "or they were randomised to aspirin or placebo [...] In this presentation, I will focus on the aspirin to placebo comparison," said Mann. Aspirin was given at a dose of 75 mg daily. In total, 5,712 participants were included in this study, and 983 of these presented with CKD at baseline. The mean follow-up was 4.6 years.

For eGFR <60 ml/min/1.73 m2, Mann revealed the benefits of aspirin compared with placebo. Importantly, there was a "reduction in risk for the primary outcome [myocardial infarction, stroke, and cardiovascular death] of 43%." However, the p value for interaction was 0.14. The researchers then divided the whole population into tertiles: eGFR values of <70, 70–90, and >90 ml/min/1.73 m2. With decreasing eGFR, the benefit of aspirin relative to placebo increased. In this case, the p value for tend was significant (0.02).

The risk of major, minor, and gastrointestinal bleeding was also investigated in all patients. Mann emphasised the "low risk of bleeding and no difference whatsoever in this trial comparing aspirin to placebo, So, bleeding was not a problem."

Finally, Mann considered the primary design of the TIPS-3 trial, which explored aspirin plus polypill in people with high cardiovascular risk and CKD. For individuals with eGFR <60 ml/min/1.73 m2, double placebo was compared with double active. Relative to double placebo, the double active regimen reduced the risk of the primary outcome by 63%.

> **"Data suggest that aspirin may moderately reduce the substantial cardiovascular burden of people with CKD but no history of cardiovascular disease"**

In conclusion, data suggest that aspirin may moderately reduce the substantial cardiovascular burden of people with CKD but no history of cardiovascular disease. Furthermore, bleeding risks may not outweigh the cardiovascular benefits of aspirin in CKD. ●

Dickkopf-3 Predicts Kidney Disease Progression in Children

URINARY Dickkopf-3 (DKK3) protein levels have been shown to predict short term estimated glomerular filtration rate (eGFR) in paediatric patients with chronic kidney disease (CKD). DKK3 is a protein released by the tubular cells whenever tubular interstitial inflammation and active changes in the tubular interstitial compartment are present and in adults. It has been associated with the risk of developing acute kidney injury (AKI), as well as CKD progression at 1 year.

The study, presented by Franz Shaefer, Professor of Paediatrics and Chief of the Paediatric Nephrology Division, Heidelberg University Hospital, Heidelberg, Germany, at the 59th ERA Congress, assessed DKK3 as a predictor of kidney disease progression in children. To do so, two separate cohorts of children was analysed: one from the 4C study, an observational study in 705 children (aged 6 to 17 years at enrolment), and the other from the ESCAPE trial, a randomised clinical trial in 385 children on a fixed dose of angiotensin-converting enzyme (ACE) inhibitors. As the hypothesis was that DKK3 might be a useful indicator of sub-acute changes in eGFR, the authors observed DKK3 urine levels every six months in patients from both studies.

Study results showed that the higher the DKK3 levels, the more rapid the loss of eGFR in both cohorts, independently of the underlying disease, proteinuria, baseline eGFR, obesity, age of the patient, or the presence of hypertension. Additionally, in the 4C study, the DKK3 levels were 50% lower in patients receiving renin-angiotensin system (RAS) antagonists, and patients with higher DKK3 levels were the ones that benefitted most from ACEi and/or angiotensin receptor blockers (ARB) therapy. In the ESCAPE cohort, the authors found that DKK3 levels predicted the nephroprotective effects of the low intensified blood pressure control, which was associated with reduced eGFR loss.

> **"DKK3 is a promising new biomarker that may predict responsiveness to nephroprotective therapies, and may become instrumental in designing risk-adapted personalised medicine approaches in pharmacological nephroprotection"**

DKK3 is a promising new biomarker that may predict responsiveness to nephroprotective therapies, and may become instrumental in designing risk-adapted personalised medicine approaches in pharmacological nephroprotection. ●

The THOMAS Study: Early Detection and Treatment for Chronic Kidney Disease

CHRONIC kidney disease (CKD) affects 10% of the population around the world. This condition can get progressively worse and result in kidney failure, as well as other serious comorbidities. Diagnostic tests for CKD usually involve examining the blood and urine for proteins that may indicate the kidneys are not functioning properly. Unfortunately, there is no cure for CKD; therefore, it is critical to detect CKD as early as possible. During the 59th European Renal Association (ERA) Congress, experts shared their findings from the THOMAS study, a randomised study investigating two strategies for early detection and treatment for CKD.

Ronald Gansevoort, Department of Nephrology, University Medical Center Groningen, The Netherlands, shared how screening for CKD has previously been limited to patients with known cardiovascular disease and hypertension; however, this means that many patients do not get screened in time, and this results in delayed treatment and the eGFR is already severely impaired.

Gansevoort and his colleagues aimed to design the first prospective study to investigate the value of screening the general population for albuminuria, the strongest risk factor for CKD progression, and determine the effectiveness of two home-based albuminuria screening techniques. One screening technique involved patients collecting a urine sample at home with a urine collection device, and sending this to a laboratory to measure the albumin creatine ratio. The other screening strategy involved patients measuring the albumin creatinine ratio at home with a dipstick reading using a smartphone application.

The study involved over 15,000 participants, aged 45–80 years, randomised to complete either screening technique. Patients that had confirmed albuminuria were invited for further screening for CKD at a facility. Participants that had high blood pressure, higher cholesterol, and other abnormalities were referred to their GP for treatment. The study discovered that both home-based screening techniques were effective and cost-efficient compared to no screening, and helped prevent the progression of CKD and cardiovascular disease.

In the speaker's closing remarks, Gansevoort acknowledged that improvements are needed in both techniques. In the strategy using the app, participation was relatively low and had too many false positives, and the implementation of care using the urine collection tube strategy could be improved. Overall, however, the study showed that screening the general population early for albuminuria should be considered.

DIAMOND Trial Examines Management of Hyperkalaemia in Patients with Heart Failure

INVESTIGATORS leading the DIAMOND trial have uncovered promising results regarding the management of hyperkalaemia for patients with heart failure. Hyperkalaemia is an elevated level of plasma potassium in the blood, defined as in excess of >5.5 mmol/L.

This late-breaking clinical trial was presented at the 59th ERA Congress, May 19th–22nd, 2022, which took place both online, and in Paris. Patrick Rossignol, Centre d'Investigation Clinique Plurithématique Pierre Drouin - INSERM CHRU de Nancy, Meurthe-et-Moselle, France; Professor of Therapeutics, University of Lorraine, Lorraine, France; and one of the investigators in the study, led the presentation.

In many cases, for patients diagnosed with, or who have a history of hyperkalaemia, treatment using renin-angiotensin-aldosterone system inhibitors (RAASi) is compromised. The study aimed to discover whether the use of patiromer, a novel potassium (K+) binder, could improve the adherence of RAASi for patients, as well as ameloriating serum K+ levels. The primary endpoint of the study is the mean difference in serum K+ between patiromer and placebo arms. Five secondary endpoints were also considered.

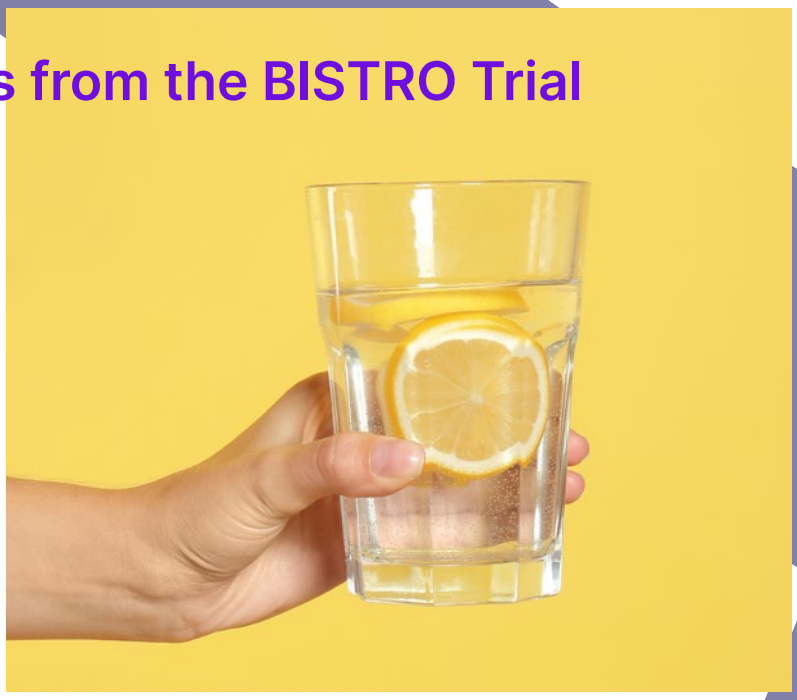
In the DIAMOND trial, around 810 individuals were enrolled, all of whom had heart failure with reduced ejection fraction <40%. Patients who met the screening criteria were entered into a single-blind, run-in phase, and either began or continued with a course of mineralcorticoid receptor antagonist (50 mg/day), RAASi therapy to >50% of target dose, and patiromer (maximum of three 8.4 g packs/day). This phase of the trial lasted for around 12 weeks. Afterwards, patients were double-blind randomised in a 1:1 ratio, and received either continued patiromer or placebo.

> **"Investigators leading the DIAMOND trial have uncovered promising results regarding the management of hyperkalaemia for patients with heart failure"**

Rossignol commented on the challenges of conducting such a trial during the COVID-19 pandemic, but went on to highlight encouraging early results. During the single-blind, run-in phase of the trial, 85% of patients were optimised. Within the placebo group, in which patiromer was withdrawn from patients, Rossignol stated: "All endpoints were statistically and convincingly positive."

The full results of the DIAMOND trial are yet to be published.

Late-Breaking Results from the BISTRO Trial



DIALYSIS is a necessary procedure for patients whose kidneys have stopped functioning properly. The procedure involves removing excess fluid and waste products from the blood using a machine. Maintaining residual kidney function results in several benefits for patients who require dialysis.

In a late-breaking clinical trial, namely the BISTRO trial, presented at the 59th European Renal Association (ERA) Congress in Paris, France, this year, Simon Davies, Centre for Science and Technology in Medicine, School of Postgraduate Medicine, Keele University, Staffordshire, UK, shared the key research question for this clinical study: can the use of bioimpedance spectroscopy help guide fluid management by avoiding dialysis-related volume depletion?

The design of the study was an open multicentre randomised controlled trial. Researchers evaluated whether taking regular measurements using a bioimpedance device provides information on body composition and improves patient outcomes. The randomisation of patients (n=439) was stratified by centre using a computer-generated concealed method. Davies explained that clinicians were instructed to avoid taking the post-dialysis weight below the normally hydrated weight as determined from the bioimpedance spectroscopy. The team also conducted a cost-effective analysis, which will be available at a later date.

In both the bioimpedance and control group, fluid assessments were taken using standardised proforma monthly for 3 months, followed by every 3 months for 2 years. In the control group, fluid assessments were blinded to the bioimpedance data. To be included in the study, patients had to pass a certain criterion, such as having >500 ml urine volume per day, and had to be able to provide consent to be included in the study. Out of the sample of patients, n=222 were allocated to bioimpedance and n=217 were in the control group. The study had more withdrawals than that expected, a total of 115 patients.

The baseline characteristics (age, sex, ethnicity) at randomisation shows there was no significant difference between the two groups. Results showed death and kidney transplantation were equivalent in both groups, and time to anuria in the bioimpedance group was slightly slower compared to the control group. The rate of developing anuria was much lower than the team had expected. There were a total of 204 adverse events for the bioimpedance group varying in severity; however, this was akin to the control group.

Davies concluded that using bioimpedance compared to the standardised fluid management protocol does not lead to better preservation of residual kidney function. Interestingly, the rate of decline in residual kidney function was less rapid than previous studies have implied, and there was no serious harm using this approach, although larger studies are required to confirm this.

Ageing in Chronic Kidney Disease

Author: Robin Stannard, Editorial Assistant

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DAY 4 of the 59th ERA Congress 2022 included an expert session on cellular ageing. In a symposium session featuring specialist insight from researchers in the field, discussions focused on the cellular processes that contribute to aging, environmental influences that correlate with ageing phenotype, and chronic kidney disease (CKD) as a model for dysregulated ageing. Exploring treatments and lifestyle changes that slow ageing and increase health span, experts also shared research underlining the importance of the microbiome and the role dysbiosis plays in triggering age-related pathways.

ERA 2022

Ageing Markers in Chronic Kidney Disease: Is It Time for Rejuvenation?

The first speaker, Katrien De Vusser, Nephrology and Renal Transplantation Research Group, Katholieke Universiteit (KU) Leuven, Belgium, opened her talk by describing ageing as a disease, stating that it was a disease that she hoped, in some years, could be curable. Age in mammals is marked by the decline of multiple separate organ systems, causing an overall deterioration that leads to dysfunction. De Vusser underlined the value of CKD as a model for studying and deepening scientific understanding of common cellular and molecular patterns associated with ageing.

Articulating cellular processes associated with ageing, De Vusser focused on cellular senescence and the causes, consequences, and role it plays in both ageing and disease. Senescence is a cellular response that limits the proliferation of aged and damaged cells. It is required for tissue homeostasis and is often triggered as a stress response to insults. Senescence is a directed cellular programme that prevents stable growth, whereby cells stop dividing yet remain metabolically active. This growth rest is accompanied by chromatin remodelling, metabolic reprogramming, increased autophagy, and, pivotally, the implementation of proinflammatory mechanisms. Two pathways play essential roles in driving a cell into senescence: P53 and P16. Both are triggered in response to DNA damage, stress, or inflammation. Upregulation of P16 leads to irreversible growth arrest. This permanent arrest works to prevent the perpetuation of DNA damaged cells and their genome. Senescence is a powerful method of tumour suppression; however, this protection comes at a cost. Aged senescent cells are not destroyed by apoptosis and accumulate over time and this accumulation drives ageing in tissues.

> **"Age in mammals is marked by the decline of multiple separate organ systems, causing an overall deterioration that leads to dysfunction"**

De Vusser analysed major disease, and age-inducing mechanisms. Firstly, increasing allosteric load, which she described as adaptation to unfavourable conditions leading to chronic activation of allosteric mechanisms, is likely to cause oxidative responses, innate immune cell activation, and chronic low-grade inflammation. Secondly, De Vusser used the interstitial sodium accumulation seen in CKD as an example of the activation of age-promoting mechanisms. Finally, the activation of 'stress resistance pathways' and impairment of anti-ageing pathways. Listing 'stress resistance pathways' such as insulin-like growth factor 1, target of rapamycin-S6K1, and forkhead box O3 for their role in cell growth, stress resistance, and energy deprivation, De Vusser emphasised the damaging effects of their activation.

Placing age-related damage in the context of disease, De Vusser used the example lupus nephritis (LN). The pathophysiology of LN presents as active immune-driven flares that are paired with interstitial fibrotic damage, which is key to determining long-term outcomes. Analysis of 40 active flare lupus kidney biopsies found no association between levels of P16 and active disease; however, chronic damage and disease were associated with increased levels of P16. Notably, 5 years after biopsy, P16 was significantly associated with poor renal function.

Furthermore, meta-analysis examination has demonstrated that patients with LN have a shorter telomere length than healthy patients, regardless of age, ethnicity, and gender. These are both clear indications of prevalent cellular senescence in LN; however, it remains unclear why this senescence occurs. De Vusser shared theories that centred on the inflammatory and oxidative environment caused within the LN kidney that are exerted through the profibrotic and proinflammatory secretome typical of senescent cells.

De Vusser closed her presentation by emphasising how little is still known about ageing as a process, highlighting the value of CKD as a model for ageing cells for further study, and reiterating that more knowledge brings us closer to a cure for ageing as a disease.

The Road to Healthy Ageing

Paul Shiels, Institute of Cancer Sciences, University of Glasgow, UK, led the second presentation, using his time to place cellular ageing within the context of the aging population. There are now more people aged over 60 than at any other time in history and this demographic is growing. However, years of healthy living have not kept pace with increasing lifespan. Shiels highlighted the huge inequities in global ageing, which relate to social deprivation, by using the example of his home city of Glasgow, which has, in certain areas, both the highest and the lowest life expectancy in Europe. Summarising, he stated that in areas of deprivation, the process of ageing happens over a shorter period.

Describing ageing as the accumulation of deficits over time, Shiels introduced the concept of the exposome. An individual's exposome being the sum total of biotic and abiotic exposures starting before conception, with epigenetic modifications, until death. The exposome's importance is underlined by three simple factors, which account for approximately 50% of global mortality: air pollution, tobacco smoke, and diet. The accumulation of allostatic load over the course of life leads to an eventual tipping point at which point you reach the 'diseasome of ageing'. Kidney disease, cancer, osteoporosis, non-alcoholic fatty liver disease are all distinct diseases with the common underpinning component of dysregulated ageing. All are associated with the hallmarks of ageing; low level chronic inflammation; diminished cytoprotective responses from nmuclear factor erythroid 2-related factor 2 (NrF2); activation of ancestral retroviral elements; changes to the microbiome; calcipotriene particle toxicity; and the accumulation of non-somatic mutations.

Returning to his example of the Glasgow exposome, Shiels highlighted the relationship between diet, the microbiome, and ageing, stating that diet is "possibly the single strongest lever to optimise human health." Drawing comparisons with carnivorous big cats, he highlighted health problems associated with diets high in red meat. Big cats are hyperphosphatemic; 87% have renal pathology, 50% have colonic tumours, and they suffer from elevated inflammatory burden. In humans, those with diets high in red meat tend to die earlier, have poorer renal function, higher incidence of colon cancer, and a strong association with a range of neurodegenerative diseases. The carnitine compound, which is found in red meat, is a substrate in the gut for microbes that produce trimethadione. In the liver, trimethadione is converted to trimethylamine-N-oxide, a metabolite highly associated with inflammation, atherosclerosis, rheumatoid arthritis, and CKD. In the deprived regions of Glasgow, an imbalanced diet is associated with phosphataemia, genomic hypomethylation, telomere shortening, and inflammation. Analysis of bacterial fragments from the microbiome in the blood stream has demonstrated a significant increase in 'unfriendly' bacteria in the guts of socially deprived groups.

Salutogenic bacteria in the gut break down phenolic acids from plant proteins creating alkyl catechols, which in turn activate NrF2, an activator of cytoprotective processes. Poor NrF2 expression is naturally associated with ageing but also with poor diet and smoking. Increased levels of pathobionts are associated with CKD; however, dietary intervention can ameliorate this situation. For example, resistant starch type 2, a prebiotic, has been demonstrated to mitigate oxidative stress in patients with CKD on haemodialysis. This simple intervention increases salutogenic gut bacteria and can induce NrF2 agonism.

Closing his presentation, Shiels emphasised that manipulating the exposome can have dramatic effects on both ageing and health span. He

further looked to the future, criticising current standards that see diseases of age treated separately, organ by organ, theorising the increased overall improvements to health span that could be made by looking at the holistic, underlying components of the aging process.

Is Food as Medicine an Option?

The third and final presentation, given by Denise Mafra, Federal Fluminense University, Niterói , Brazil, provided further depth to the relationship between diet and the ageing phenotype. Discussing inflammation as a key cause of ageing, Mafra, detailed the molecular pathways involved. The activation of nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and high production of reactive oxygen species (ROS) causes NF-κB translocation to the nucleus, where the molecule promotes increased production of inflammatory cytokines. NrF2 is a master regulator of cytoprotective responses. In a healthy situation there should be some production ROS, balanced with antioxidant responses that is controlled by NrF2.

A 2014 study demonstrated that patients with CKD on haemodialysis had a significantly increased expression of NF-κB compared with healthy individuals, with reduced NrF2 expression. Furthermore, gut inflammation contributed to an increased production of uraemic toxins and decreased short chain fatty acids, further activating NF-κB. These factors all link to the premature ageing phenotype of increased ROS, telomere shortening, DNA damage, cell cycle arrest, and senescent cells.

Mafra highlighted that food can reduce NF-κB and improve NrF2 production, with a good diet correlated with positive bioactive compounds, producing a balanced gut microbiome with increased short chain fatty acids and decreased uremic toxin. Listing positive foods and compounds such as suffurophane, beetroot, brazil nuts, fermented food, ginger, and garlic, she emphasised the need for further studies. Many of the positive cellular anti-ageing effects of these foods have only been demonstrated *in vitro* in mouse or in small-scale human studies. Large-scale clinical trials are needed to fully comprehend and act upon the possible benefits that these foods might provide.

Conclusion

Focusing on the cellular process of ageing, the experts were able to highlight the association between environmental influences and human health over time. Using CKD as a model for ageing allowed the researchers to explain the influence of individual molecules and explore possibilities of future treatments or mitigating diet choices. However, all experts highlighted how little is still understood about the processes behind ageing and the lack of evidence in the form of clinical studies to support potential mitigating dietary and medical therapies.

The Dual Role of Endothelin-1 and Angiotensin II in Disease Progression of Focal Segmental Glomerulosclerosis and IgA Nephropathy

This article details the diagnosis and treatment of IgA nephropathy and focal segmental glomerulosclerosis, as discussed in a symposium delivered as part of the European Renal Association (ERA) 59th Congress in Paris, 19th–22nd May 2022

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Meeting Summary

IgA nephropathy (IgAN) and focal segmental glomerulosclerosis (FSGS) are rare primary glomerulopathies, though the incidence of IgAN is greater. Endothelin 1 (ET-1) and angiotensin II (Ang II) are implicated in the development and progression of IgAN and FSGS. Both conditions impact health-related quality of life (HRQoL) and may lead to kidney failure. IgAN and FSGS are both evidenced clinically by proteinuria, with a greater degree of such associated with more progressive disease and shorter times to kidney failure. Accordingly, the reduction of proteinuria in patients with these conditions is a key target. Currently, IgAN and FSGS treatments are unsuccessful or only partially successful in a number of patients. Immunosuppressant therapy is first-line for primary FSGS and utilised

for patients with IgAN who remain at high risk of progression despite maximal supportive care; however, while effective, there is a significant risk of toxicity and relapse is frequent. A number of clinical trials are ongoing to investigate the use of non-immunosuppressive agents in the management of these conditions. The dual endothelin Type A receptor/Ang II subtype 1 receptor (ET_AR/AT_1R) antagonist (DEARA) sparsentan is currently being assessed as a means to control kidney disease progression. Interim study results show that sparsentan can lead to greater reductions in proteinuria than AT_1R antagonism alone in IgAN and more patients reaching partial remission (PR) in FSGS.

Herein, a symposium by leading experts at the European Renal Association (ERA) 59th Congress in Paris, 19th–22nd May 2022, is presented. It highlights IgAN and FSGS and the role of proteinuria in these conditions, and how targeting ET-1 and Ang II can lead to a reduction in proteinuria in IgAN and potential FSGS PR.

Introduction

Primary glomerulopathies include IgAN and FSGS, both of which are diagnosed following kidney biopsy.[1] One clinical sign associated with higher progression rates of kidney disease, kidney failure, and death in these conditions is proteinuria.[2,3] As such, the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases states that proteinuria has disease-specific relevance for prognosis and treatment decision-making in glomerular disease.[1]

Herein is a summary of a symposium delivered at the ERA 59th Congress, where Loreto Gesualdo, Nephrology, Dialysis and Transplantation Unit, Azienda Ospedaliero Universitaria Consorziale Policlinico, University of Bari, Italy, first discussed the clinical significance of proteinuria in IgAN therapy; and then Sian Griffin, Department of Nephrology and Transplantation, University Hospital of Wales, Cardiff, UK, evaluated proteinuria with respect to FSGS. Finally, Pierre-Louis Tharaux, Institut National de la Santé et de la Recherche Médicale (Inserm), Université Paris Cité, Paris Cardiovascular Center (PARCC), France, discussed the role of the peptide ET-1 and the hormone Ang II in both IgAN and FSGS, and described how targeting these pathways reduce proteinuria and could promote long-term kidney health.

Spotlight on IgA Nephropathy: Clinical Significance of Proteinuria

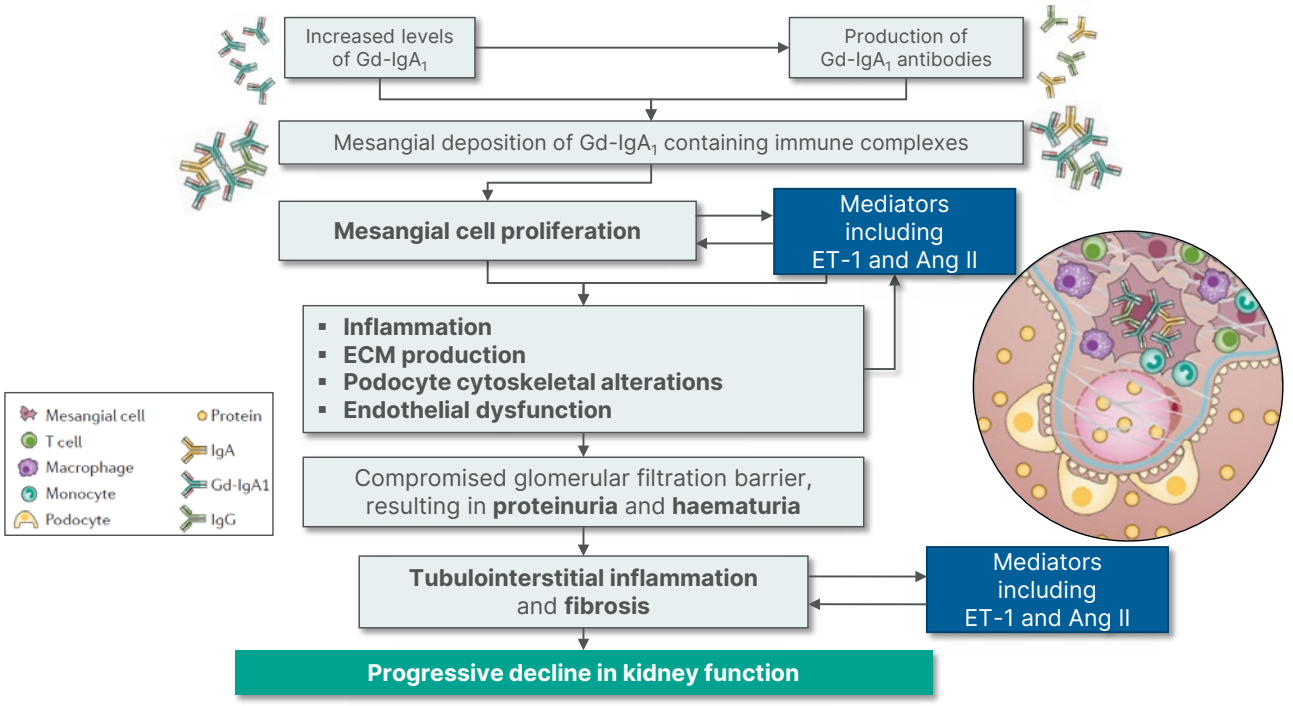
Loreto Gesualdo

Though rare, the immune-complex mediated glomerular disease IgAN is one of the most prevalent primary glomerulonephritis worldwide. Although peak incidence occurs in the third and fourth decades of life, IgAN can occur at any age. Incidence rates vary widely according to how IgAN is assessed, from between 0.03–4.5/100,000 persons/year in children and teenagers and 0.2–5.7/100,000 persons/year in the general population (including children).[4,5] In one study, there was a 1.53-fold increased risk in all-cause mortality and a 6-year reduction in life expectancy compared with age/sex matched controls.[6] In another, 53% of patients with primary IgAN developed kidney disease or died within a median follow-up time of 9.2 years.[7]

IgAN can profoundly impact a person's quality of life due to symptoms, such as pain and fatigue, and is associated with depression and anxiety,[8] which are often related to uncertainty and complications with therapy.[9] In patients who progress to kidney failure, HRQoL is even more affected, with substantial adverse effects on mental health and physical functioning.[10-12]

As shown in Figure 1,[9,13,14] increased levels of galactose-deficient IgA1 (Gd-IgA1) in IgAN lead to increased production of Gd-IgA1 antibodies, both of which can increase mesangial cell deposition of Gd-IgA1-containing immune complexes. This results in mesangial cell activation and proliferation, which both stimulates and is

Figure 1: Decline in kidney function in IgA nephropathy.



Ang II: angiotensin II; ECM: extracellular matrix; ET-1: endothelin 1; Gd-IgA1: galactose-deficient IgA1.

stimulated by mediators including Ang II and ET-1. A pathological cycle can occur whereby downstream consequences of these processes, including inflammation, extracellular matrix production, podocyte cytoskeletal alterations, and endothelial dysfunction, may also lead to increased mesangial cell proliferation as well as Ang II and ET-1 production. The result is a compromised glomerular filtration barrier and subsequent proteinuria and haematuria, leading to tubulointerstitial inflammation, fibrosis, and, ultimately, progressive decline in kidney function.[9,13,14]

Gesualdo explained that because the estimated glomerular filtration rate (eGFR) decreases with increasing proteinuria, it is recommended that both factors be taken into consideration when assessing kidney function.[1] The rate of decline in kidney function in IgAN is most strongly predicted by sustained proteinuria, with each incremental g/day >1 g being associated with a 10- to 25-fold more rapid rate of kidney function decline and similar differences in kidney survival.[15]

The goal of therapy in IgAN, in accordance with the KDIGO guidelines, is to slow the rate of progression to kidney disease through management of proteinuria to at least <1 g/day, and blood pressure to <120 mmHg systolic blood pressure. With this in mind, proteinuria has now been incorporated into a risk stratification protocol through the International IgAN Prediction Tool, as recommended by the KDIGO guidelines.[1] This tool incorporates clinical and histologic data to provide a prognosis at the time of biopsy to help identify patients at high risk of rapid disease progression and requiring urgent care to protect kidney function.[1,16,17]

Magnitude and duration of proteinuria reduction have been shown to impact long-term clinical endpoints in IgAN. For instance, a retrospective, multi-ethnic cohort study found that each 3-month period of proteinuria remission (defined as ≥25% reduction in proteinuria from peak value after biopsy and an absolute reduction in proteinuria to >1 g/day) was associated with a 9% relative risk reduction in kidney failure or a 50% reduction in eGFR decline over a median follow-up of 3.9 years.[18]

In addition, an analysis of patient registry data predicted that a 30% reduction in proteinuria could lead to a 50% lower risk of kidney failure and an increase in median time to kidney failure from 12.4 to 23.1 years.[19] Proteinuria has successfully been used in clinical studies as a surrogate endpoint for the effect of treatment on slowing progression to kidney failure, as evidenced by a meta-analysis of 13 controlled trials that showed an association between the effect of treatment on proteinuria and treatment effects on a composite of the time to the first occurrence of a doubling of serum creatinine level, kidney failure, or death.[20]

Gesualdo noted, however, that there remains a high unmet clinical need in IgAN therapy, with approximately half of all patients remaining at high risk of progression due to proteinuria levels of >0.75–1.00 g/day for ≥90 days[1] despite 3 months of therapy.[1,21,22] The KDIGO guidelines for the management of glomerular diseases indicate that patients with IgAN who remain at high risk of progressive chronic kidney disease despite maximal supportive care can be considered for a 6-month course of immunosuppressive therapy with corticosteroids. However, the risk/benefit profile of glucocorticoids must be individually discussed for those with eGFR ≥30 mL/min/1.73^2, and maximal supportive care should be considered for patients with eGFR 30 mL/min/1.73^2.[1]

Angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) are also recommended for the treatment of IgAN. However, condition-specific studies are limited, and data supporting their use are of low to moderate quality.[1] There is also debate over whether renin-angiotensin system (RAS) blockade with ACEis/ARB alone is sufficient, or whether therapy should also include immunosuppression.[23,24]

In the TESTING study, over a mean 4.2-years follow-up, the hazard ratio for the primary endpoint (40% decline in eGFR, kidney failure, or death due to kidney disease) was 0.53 (95% confidence interval: 0.39–0.72; p<0.001) for those receiving methylprednisolone (n=136) compared with a placebo group (n=126). However, serious adverse events were more frequent with methylprednisolone (10.9%) versus placebo (2.8%), especially in those with full-dose therapy (maximum 48 mg/d), where figures were 16.2% and 3.2%, respectively.[25] However, as corticosteroid therapy carries a significant risk of toxicity, this approach should be avoided in susceptible patients,[1,24,26] while there is also an increased risk of infections in IgAN with the use of steroids and other immunosuppressants.[24,26]

Several Phase III trials are currently investigating novel therapeutic approaches to target proteinuria in IgAN. The DEARA sparsentan is being investigated in the PROTECT trial, in which the primary interim endpoint (PIE) is a change in urinary protein-to-creatinine ratio (UP/C) from baseline to Week 36. In this 114-week study, with an open-label extension period of up to 156 weeks, approximately 404 patients with persistent overt proteinuria who remain at high risk of disease progression despite therapy have been randomly assigned in a 1:1 ratio to either sparsentan or irbesartan (an ARB).[27]

Other studies include the delayed release of budesonide that is being investigated in the NEFIGARD trial, which has a PIE of change in UP/C from baseline to 9 months.[28] This corticosteroid has recently received accelerated approval by the U.S. Food and Drugs Administration (FDA).[29] Narsoplimab, a mannan-binding lectin serine protease 2, is being investigated in the ARTEMIS-IgAN trial, which has a PIE of change in 24-hour urine protein excretion from baseline to Week 36,[30] while the APPLAUSE-IgAN trial of the factor B inhibitor (alternative complement pathway), iptacopan (LNP023), has a PIE of ratio of UP/C from baseline to 9 months.[31] Finally, the ET_AR antagonist atrasentan is being investigated in the ALIGN trial, with a PIE of change in UP/C ratio from baseline to Week 24.[32] "After 25 years," concluded Gesualdo, "finally we're getting [...] new drugs that may change the natural history of IgANs."

Spotlight on Focal Segmental Glomerulosclerosis: Clinical Significance of Proteinuria

Sian Griffin

FSGS is uncommon, with a global incidence of 0.8/100,000/year depending on study and

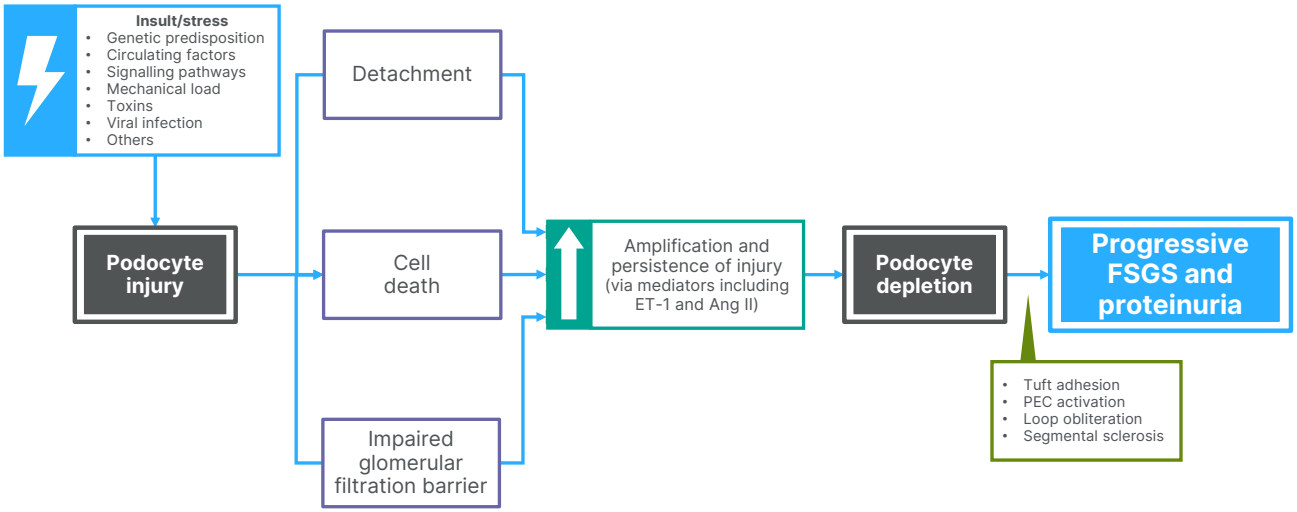
clinical assessment.[5] Griffin noted that the condition has a significant impact on patients. An estimated 15% of glomerular disease diagnoses in Europe are due to FSGS,[33] and it accounts for approximately 20% of paediatric and 40% of adult nephrotic syndrome cases, the larger figure of the latter being due to greater heterogeneity of causes.[34,35] This is of concern as kidney failure occurs in up to 45% of cases over 10 years and is associated with an increase in mortality.[36]

Griffin described how the profound impact of nephrotic syndrome is seen on the lives of patients in her clinic, and can be especially devastating for children and young adults and during pregnancy. Studies have revealed that the impact includes physical symptoms, such as shortness of breath, severe oedema, and fatigue,[37,38] as well as an increased risk of cardiovascular problems, such as acute coronary syndrome, heart failure, venous thromboembolism, and death.[35] FSGS has also been shown to lead frequently to HRQoL issues such as anxiety, depression, poor sleep, and a reduced ability to socialise.[37] Pregnancy carries a significant risk to patients with FSGS, as well as the fetus.[1] As such, Griffin noted that patients with FSGS require counselling to understand the disease and its potential consequences.

As can be seen from Figure 2,[14,39] the site of primary injury in FSGS is the glomerular podocyte. Such injury can arise from internal (genetic predisposition, unknown circulating factors, disrupted signalling pathways, and mechanical load) or external (toxins including anthracyclines, mechanistic target of rapamycin inhibitors, and anabolic steroids, and viral infections such as HIV and cytomegalovirus) factors.[14,39] The podocyte, according to Griffin, is usually a very resilient cell, but injury can lead to detachment from the underlying membrane, cell death, and an impaired glomerular filtration barrier. There is a critical threshold of podocyte loss, but amplification and persistence of injury (via inflammatory mediators including ET-1 and Ang II) can lead to podocyte depletion as it is a terminally differentiated cell with little or no regeneration capacity. This results in large areas of bare basement membrane and connections formed with overlying parietal epithelial cells, which can become activated. There is also ongoing inflammation with obliteration of the capillary loop and segmental sclerosis. This can be seen histologically as progressive FSGS and manifests clinically as proteinuria.[39]

In 2021, the KDIGO guidelines for the management of glomerular diseases were updated so that FSGS is classified based

Figure 2: Podocyte injury and depletion in focal segmental glomerulosclerosis.



Ang II: angiotensin II; ET-1: endothelin 1; FSGS: focal segmental glomerulosclerosis; PEC: parietal epithelial cell.

on proteinuria, aetiology, and histological presentation of a biopsy. Primary FSGS is the classical cause associated with circulating factors, as evidenced by successful treatment by plasmapheresis in rapid and recurrence of FSGS following kidney transplantation.[1] This typically presents abruptly with FSGS lesions, extensive foot process effacement, and nephrotic syndrome (proteinuria >3.5 g/d, hypoalbuminemia <30 g/L, and potentially accompanied by dyslipidaemia and oedema). Secondary FSGS may present similarly to primary FSGS, but lesions will be accompanied by an FSGS-causing pathophysiologic process such as a hyperfiltration injury or diabetes. Genetic FSGS occurs in patients who have podocyte or glomerular basement membrane protein mutations. There are also cases of FSGS with no identifiable cause and absence of nephrotic syndrome.[1]

As in IgAN, persistent proteinuria in FSGS is a risk factor for progressive kidney failure, with severity of proteinuria being associated with a faster time to kidney failure. For instance, while less than 15% of patients with non-nephrotic proteinuria progress to kidney failure in 10 years, at least 50% of patients with nephrotic proteinuria (>3 g/d) progress to end-stage renal disease in 5–10 years, with an average time to end-stage renal disease in patients with high levels of proteinuria (>10–14 g/d) of 2–3 years.[40]

Kidney survival is greatly improved when proteinuria is controlled. For example, in one study (n=338) where complete (≤0.3 g/d) or partial (>50% reduction to <3.5 g/d; or reduction to <2 g/d) proteinuria remission was achieved in 26% and 25% of patients, respectively. Kidney survival was significantly better at 5, 10, and 15 years follow-up compared with no remission.[41]

However, patients with FSGS with only PR are more likely to have poorer kidney outcomes, as evidence in a study where 52% of 117 patients with PR relapsed after a median 7 months, compared with 36% of 55 patients with complete remission who relapsed after a median time of 20 months. Relapse in the PR group was significantly associated with worsening kidney function (p=0.03) and a higher risk of kidney failure compared with patients who achieved PR with no relapse (hazard ratio: 2.90; 95% confidence interval: 1.09–7.72; p=0.03).[42]

Griffin observed that it is of particular interest to stratify further patients who achieve PR to understand the factors associated with better long-term survival. Data on 466 well-characterised children and adults with FSGS and proteinuria across a range of ethnic groups revealed that, while the conventional definition of PR was UP/C <3.5 g/g and a 50% reduction in UP/C, a more robust FSGS PR endpoint (FPRE) of UP/C 0.3 to <1.5 g/g and a ≥40% reduction in UP/C was associated with a better long-term outcome and reflects an earlier predictor of kidney survival in FSGS.[43] Griffin noted that this is important in the context of clinical trials because "what we want when assessing new agents is good surrogate markers that will predict long-term outcomes for our patients."

The FPRE has been further validated in a trial of 270 paediatric and adult patients with FSGS and nephrotic-range proteinuria (≥3.0 g/g), where lower proteinuria levels were associated with a 13-year extended median time to kidney failure or death. Here, reported Griffin: "In a retrospective analysis of an observational study, it was found that there were no differences in long-term outcomes between patients having a complete response and those with the robust measure of PR [FPRE], and so these were compared with patients who did not have a PR as defined by these criteria [<1.5 g/g and ≥40% reduction from baseline]. By grouping patients in this way, a significant benefit is seen for those patients who achieve either of these endpoints [complete remission and/or FPRE], compared to those patients who do not."[44] During the panel discussion, Griffin conferred how the FPRE can also be used in the clinic as a measure to inform patients as to whether they are more or less likely to progress to kidney failure.

Despite recent advances, there remains an unmet need in FSGS for more efficacious treatments with a favourable safety profile. According to KDIGO recommendations, ACEis and ARBs are standard of care along with first-line high-dose oral glucocorticoids or calcineurin inhibitors, despite the lack of evidence from randomised controlled trials.[1] As long periods of immunosuppressant therapy are required,[40] there is a significant risk of toxicity.[1] Further, relapse is common with all current therapeutic options, and a substantial number of FSGS patients do

not achieve proteinuria remission and remain at a high risk of progressive kidney disease.[1,42,45,46]

To advance therapeutic options in FSGS, two Phase III trials are currently investigating novel therapies. Sparsentan is being investigated in the DUPLEX study, which has a PIE of the proportion of patients achieving a UP/C ≤1.5 g/g and a >40% reduction from baseline in UP/C (FPRE) at Week 36.[47] In addition, the C-C chemokine receptor type 2 inhibitor DMX-200 is being investigated in the ACTION3 study, which has a PIE of percent change in urine UP/C (based on 24-hour urine collection) from baseline to Week 35.[48]

Evidence for the Dual Role Endothelin 1 and Angiotensin II in Proteinuria and Chronic Kidney Disease Progression in IgA Nephropathy and Focal Segmental Glomerulosclerosis

Pierre-Louis Tharaux

The peptide ET-1 is the most biologically relevant endothelin to kidney physiology. It is a highly stable molecule and an extremely potent vasoconstrictor with long-lasting effects.[49] ET-1 is produced most prominently in the kidney with G-protein coupled endothelin receptors B ubiquitously expressed therein, depending on location.[50] Both receptors are expressed in the afferent and efferent arterioles, and podocytes; mesangial cells primarily express ET_AR; and, the proximal tubule, cortical and inner medullary collecting ducts, thick ascending limb, and vasa recta capillary primarily express endothelin receptor B.[49,50]

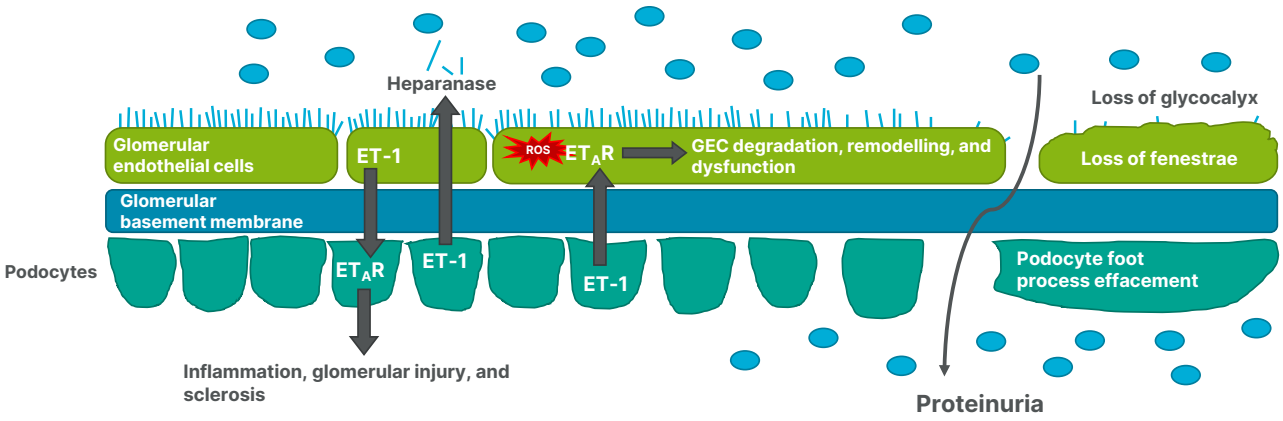
Tharaux discussed how experimental evidence indicates that podocyte functional cytoskeletal dynamics are altered when stimulated by ET-1, promoting cell detachment and loss of podocyte foot processes (Figure 3).[51-54] The podocyte can also produce heparanase, an enzyme that cleaves the endothelial glycocalyx, the first layer of the glomerular filtration barrier that ensures selectivity against proteinuria in the glomerulus. Endothelial cells also react to enhanced ET-1 signalling with resulting production of reactive oxygen species, the opening of endothelial junctions, and degradation of the endothelium.[51-54] As discussed in previous sections, ET-1 can act in tandem with Ang II, leading to the amplification of the ongoing inflammatory cytokine response, direct podocyte injury, and vascular dysfunction, including excessive glomerular capillary pressure. These actions can worsen glomerular injury and proteinuria, driving tubular damage and fibrosis, culminating in progressive disease.[14,52]

ET-1 promotes chronic kidney disease via activation of ET_AR (Figure 3),[52-54] and several studies have suggested a role for ET-1 in FSGS and IgAN. For example, urinary ET-1 is elevated in primary FSGS,[55] as is ET_AR staining in kidney cells, primarily in the glomerular endothelial cells.[56] In IgAN, a kidney biopsy study revealed that ET-1 expression in glomeruli and proximal tubular epithelial cells was significantly greater in patients with higher-grade (≥2 g/24 hrs) than lower-grade (<2 g/24 hours) proteinuria or controls.[57] This has been correlated with proteinuria and 1-year progression in IgAN.[57,58] Studies have also shown that in patients with IgAN, neutrophils stimulate mesangial cell production of ET-1[59] and monocytes have increased ET-1 expression.[60]

Targeting of the ET-1 pathways may lead to proteinuria reduction. For example, in a murine model of IgAN, ET_AR antagonism reduced proteinuria and downregulated pro-inflammatory, pro-fibrotic, and pro-sclerotic pathways.[61] In FSGS and IgAN, combined RAS blockage and ET_AR inhibition has been shown to achieve a substantial anti-proteinuric effect.[62,63] Clinical evidence (as provided by the RADAR and SONAR studies of patients with proteinuria plus diabetic nephropathy or Type 2 diabetes, respectively) shows that selective ET_AR antagonism with atrasentan, on a background of maximal RAS inhibition, can significantly decrease proteinuria[64] and reduce the risk of kidney failure.[65]

As a DEARA, sparsentan has regions with affinity for both ET_AR and AT_1R, and can bind individually to either receptor to inhibit intracellular signalling.[14,66] In the PROTECT study in patients with IgAN, interim results showed that sparsentan reduced proteinuria to a greater extent than the AT_1R antagonism alone with irbesartan (49.8% versus 15.1% reduction from baseline in UP/C at Week 36; $p<0.0001$).[67] In the DUPLEX study interim results, a greater

Figure 3: Podocyte and glomerular endothelial cell interaction via endothelin-1 can result in glycocalyx loss and altered podocyte cytoskeletal dynamics.



ET-1: endothelin 1; ET_AR: endothelin A receptor; GEC: glomerular endothelial cells; ROS: reactive oxygen species.

proportion of patients with FSGS achieved FPRE (UP/C ≤1.5 g/g and >40% reduction in UP/C from baseline) with sparsentan than with irbesartan (42% versus 26% of patients at Week 36; p=0.0094). Preliminary safety analysis found a profile similar to irbesartan.[68] In both studies, preliminary reviews of interim data showed that the safety profile of sparsentan was consistent with previous observations, that it was generally well tolerated, and that no new safety signals had emerged.[67,68]

Conclusion

The presentations in this symposium highlighted how proteinuria is an important measure in IgAN and FSGS, with elevated protein levels being the single strongest prognostic indicator for disease progression in both.[15] Complete or partial remission of proteinuria is associated with more favourable outcomes[18,41,] and treatment should be aimed at achieving these goals.[1] However, there are still a number of patients who remain at high risk of disease progression despite first-line treatment approaches.[21,22] In FSGS, application of the novel measurement of FPRE is associated with better long-term outcomes and allows for earlier prediction of kidney survival,[43,44] while in IgAN, the IgAN Prediction Tool is recommended to aid prognosis.[1,16,17]

Several Phase III trials are investigating a range of novel therapeutic approaches to address proteinuria in IgAN and FSGS, including those that target ET-1 and Ang II,[27,28,30-32,47] which act in tandem to worsen glomerular injury and proteinuria.[9,13,14,39] After a paucity of treatments for these conditions, it is hoped that new therapies will add to treatment choices.

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Medium Cut-off Delivering Expanded Haemodialysis Therapy: Improving Clinical and Economic Outcomes in the Real World

This symposium took place on 21 May 2022 as part of the 59th Annual Congress of the European Renal Association (ERA)

Chairpeople:	Mario Cozzolino Renal and Dialysis Unit, ASST Santi Paolo e Carlo and Department of Health Sciences, University of Milan, Italy
Speakers:	Peter Stenvinkel,[1] Jernej Pajek,[2] Jarrin D. Penny[3,4] 1. Department of Renal Medicine, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden 2. University Medical Centre, Ljubljana, Slovenia 3. Western University, London, Ontario, Canada 4. Kidney Clinical Research Unit, Lawson Health Research Institute, London Health Sciences Centre, London, Ontario, Canada

Disclosure:	Cozzolino has participated in scientific advisory boards for Amgen, AstraZeneca, Baxter, GlaxoSmithKline, and Vifor Pharma, and has lectured at scientific meetings sponsored by Amgen, AstraZeneca, Baxter, Fresenius Medical Care, and Vifor Pharma. Stenvinkel has participated in scientific advisory boards for AstraZeneca, Baxter, Fresenius Medical Care, GlaxoSmithKline, Reata, and Vifor, and has lectured at scientific meetings sponsored by Astellas, AstraZeneca, Baxter, Fresenius Medical Care, Novo Nordisk, and Pfizer/Bristol-Myers Squibb. Pajek has received research grants and speaker fees from Baxter Healthcare. Penny has been a speaking consultant for Baxter, has received study sponsorship from Baxter Canada, and has received research funding from Baxter Healthcare, Kidney Foundation of Canada, London Health Sciences Centre, Satellite Healthcare, and the Western Graduate Research Scholarship.
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Meeting Summary

This symposium took place during the 59th Annual Congress of the European Renal Association (ERA), held in Paris in May 2022. Peter Stenvinkel, Department of Renal Medicine, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, presented the pathological background of the association between the uremic milieu and inflammation and pathways for

poor outcomes in patients on haemodialysis (HD). He described approaches to combat uremic inflammation, including interventions to decrease the production of inflammatory molecules and strategies to increase removal of inflammatory molecules by improved dialytic clearance using expanded haemodialysis (HDx) with a medium cut-off (MCO) membrane. Stenvinkel articulated that there are larger-middle molecular weight uremic molecules that are not removed by current dialysis strategies and that are associated with clinical outcomes, such as atherosclerotic cardiovascular (CV) disease, structural cardiac disease, and immunodeficiency. These molecules form a relevant group of uremic toxins to potentially be removed using MCO membranes. Stenvinkel also emphasised that dialyser loss is not the main factor for low serum albumin, and the latter is a predictor of poor outcome only in cases of high C-reactive protein (CRP). Finally, hypoalbuminemia predisposes to higher morbidity and mortality only in the presence of inflammation. Jernej Pajek, University Medical Centre, Ljubljana, Slovenia, explained that the predominant single causes of hospitalisation in patients with end-stage renal disease (ESRD) are CV causes and infections, and he explored the scientific plausibility for mechanisms linking CV disease, infections, and hospitalisation in patients on dialysis. He discussed studies evaluating intermediary mechanisms, indicating that dialysis with an MCO membrane may lead to lower CV morbidity and mortality, and described hard endpoint data that showed reduced hospitalisation rates with HDx compared with haemodialysis (HD). Jarrin D. Penny, Western University, London, Ontario, Canada, and Kidney Clinical Research Unit, Lawson Health Research Institute, London Health Sciences Centre, London, Ontario, Canada, discussed the importance of patient-reported outcome measures (PROM) in the management of patients on dialysis. She demonstrated the results from a dynamic PROM tool, demonstrating improvements in several parameters after patients were switched from high-flux HD to HD with an MCO membrane. Penny shared compelling testimonials alongside the changes in PROMs, in which patients described improvements in overall quality of life (QoL), general wellbeing, energy, sleep quality, appetite, pruritus, and restless legs with HDx compared with HD. She also discussed a patient case in which extensive itch and associated poor sleep, anxiety, and reduced QoL were greatly improved by 12 weeks of HDx. A patient described his experience of symptom improvement with HDx, symptoms returning on switching to HD, and again improving on reinitiation of HDx.

Uremic Toxins and Inflammation

Peter Stenvinkel

Stenvinkel explained that the survival of patients on HD is significantly lower compared with the general population.[1] There is regional variation in the risk of death in these patients, with significantly lower risk in China[2] and Japan,[3,4] two countries with a documented lower prevalence of inflammation, compared with the USA[5,6] and Europe.[7]

Patients with chronic kidney disease (CKD) undergo premature ageing, including muscle wasting, osteoporosis, vascular calcification, and CV hypertrophy.[8] According to Stenvinkel, inflammation has a role in this ageing process as it inhibits anti-ageing mechanisms and anabolic pathways, stimulates catabolic pathways, and, in concert with sympathicovagal imbalance and epigenetic changes with DNA damage, drives the premature ageing phenotype. Stenvinkel underscored how closely related inflammation is to telomere attrition, a main driver of premature ageing processes.[9]

Stenvinkel outlined that the causes of inflammation include exogenous factors such as central venous catheters, dialysis treatment, and gut dysbiosis; cellular factors such as cellular senescence and oxidative stress; tissue factors, such as sodium and fluid overload, and tissue hypoxia; and a plethora of uremic toxins such as

calcium phosphate and indoxyl sulfate, which are major drivers of uremic inflammation.

Approaches to combat uremic inflammation include interventions aimed to decrease the production of inflammatory molecules. Stenvinkel highlighted lifestyle interventions, such as physical exercise and smoking cessation, and expressed a particular interest in the use of food as a medicine to reduce inflammatory markers (e.g., a balanced diet with low inflammatory potential) by bioactive nutrients. He also noted that some commonly used drugs have anti-inflammatory potential (e.g., statins, antidepressants, angiotensin-converting enzyme [ACE] inhibitors). Other strategies aim to increase the removal of inflammatory molecules, such as the use of targeted anti-inflammatory drugs, including N-acetylcysteine, bardoxolone, and anti-cytokine agents, and improved dialytic clearance using online haemodiafiltration (OL-HDF) and HDx.

Stenvinkel specified that uremic toxins affect virtually all organs in the body, contributing to issues such as kidney and CV damage, insulin resistance, infection, inflammation, intestinal dysbiosis, and cognitive impairment, which leads to reduced QoL and increased mortality.[10]

Uremic toxins found to have the highest toxicity evidence score include IK-6, TNF, and kynurenines.[11] Stenvinkel explained that the current uremic toxins classification, however, does not help clinicians prescribe a dialysis regimen for patients with restless legs, nausea, cramps, fatigue, sexual dysfunction, pruritus, or prolonged recovery time after a dialysis session.[10] He also emphasised that uremic solutes that are relatively large compared with urea (i.e., middle molecules such as p-Cresol sulfate and β_2-microglobulin) are poorly cleared in conventional thrice-weekly HD, even with high-flux dialysers.[12] Stenvinkel also pointed out that there are larger middle molecules that are not currently removed by dialysis strategies. These include fibroblast growth factor (FGF) 23, a hormone that helps to mitigate hyperphosphatemia in patients with kidney disease,[13] and chitinase-3-like protein 1 (YKL-40), a protein secreted by macrophages, neutrophils, chondrocytes, endothelial cells, vascular smooth muscle cells (VSMC), and cancer cells.[14] FGF 23 and YKL-40 are two independent predictors of poor outcome in patients with renal disease who are undergoing dialysis.[13,14]

Endogenous molecules that are dependent on kidney clearance are water soluble (<80% protein-bound) and are categorised by size, with biomarkers of known toxicity as shown in Table 1.[10]

Table 1: Endogenous molecules dependent on kidney clearance.[10]

Category of molecules	Size (kDa)	Biomarker of known toxicity	Removal of biomarkers
Small	<0.5	Urea	Low-flux HD
Small–middle	0.5–15.0	β2-microglobulin	High-flux HD
Medium–middle	>15–25	κ-FLC	High-flux HDF
Large–middle	>25–58	λ-FLC	MCO HDx
Large	>58–170	Modified albumin	HCO HD

FLC: free light chain; HCO: high cut-off; HD: haemodialysis; HDF: haemodiafiltration; HDx: expanded haemodialysis; MCO: medium cut-off.

Stenvinkel proposed that studies are needed to test how changes in these biomarkers impact QoL. Exogenous (gut-derived) uremic toxins that are dependent on kidney clearance are small (<0.5 kDa) and ≥80% protein-bound molecules, such as homocysteine, p-Cresol sulfate, and kynurenines.[10]

The medium and large middle molecules are of clinical relevance as they have a role in atherosclerotic CV disease, structural cardiac disease, immunodeficiency,[15] protein energy wasting,[16] and systemic inflammation.[17-19] Stenvinkel articulated that there are several larger middle molecules that are not removed by current dialysis methods, and that these form a relevant group of uremic toxins to potentially be removed using MCO membranes.[20]

In a randomised controlled trial of 172 patients, the reduction ratio for removal of λ-free light chain (FLC), κ-FLC, β_2-microglobulin, complement factor D, and TNF was statistically significantly superior ($p<0.001$) for the MCO dialyser, Theranova 400 (Baxter Healthcare, Illinois, USA) compared with the high-flux dialyser, Elisio-17H (Nipro Group, Osaka, Japan).[21] Stenvinkel summarised that HDx with the MCO dialyser was safe and efficacious, providing superior removal of larger middle molecules, including several putative uremic toxins, compared with a similar size high-flux dialyser.[21]

Stenvinkel also emphasised that hypoalbuminemia per se is not an independent predictor of increased mortality in dialysis patients, but in combination with inflammation it is a sign of poor prognosis.[22] He noted that there is considerable albumin loss of 9–23 g associated with 4 hours of conventional HD with high cut-off membranes[23] compared with only 2–4 g with MCO membranes.[24] Stenvinkel observed that, on a weekly basis, albumin loss with MCO membranes is of similar magnitude to that in the urine of patients with macroalbuminuric Type I diabetes (1.3 g/day).[25] In the presentation, studies[26-30] were identified that evaluated the impact of albumin loss on serum albumin levels, and Stenvinkel noted that there was an association between albumin loss and decreased serum albumin in only four[26,28-30] of the seven patient populations studied.[22]

There is considerable interest in the predictive impact of serum albumin. A study of 822 patients grouped according to albumin and CRP levels showed that after correcting for all possible confounding factors (such as age, sex, blood pressure, diabetes, smoking, subjective global assessment of nutritional status, and renal function), low serum albumin was a risk predictor only when there was concomitant high CRP.[31] Stenvinkel concluded that inflammatory status should always be taken into account when using serum albumin for risk assessment in patients with CKD.[31]

Stenvinkel summarised the findings from HD and peritoneal dialysis (PD) studies. He explained that HD studies have shown that dialysis treatment modalities associated with improved outcomes have larger membrane surface and pore size, higher convective volumes, and transmembrane pressure, and are also associated with increased albumin loss into the dialysate.[32] However, PD studies have shown that the pronounced daily protein losses (5–7 g/day) with this dialysis treatment modality rarely affect serum albumin levels.[27] Furthermore, baseline peritoneal albumin and protein clearances are associated with signs of comorbidity, but do not have a measurable effect on patient survival.[33]

It can be speculated that albumin loss during dialysis may even be potentially beneficial because albumin is a major carrier for several small, protein-bound uremic toxins that are associated with endothelial dysfunction, and allowing some albumin loss into dialysate may increase their removal.[34] In addition, irreversible post-translational modifications of albumin such as carbamylation, oxidation, and glycosylation are pronounced in the toxic uremic milieu; therefore, allowing some leakage into the dialysate and stimulation of functional production of unmodified hepatic albumin could be beneficial.[34]

Stenvinkel concluded that several middle molecule uremic solutes, particularly the larger middle molecules, promote systemic inflammation, and some are not removed by current dialysis strategies. Dialyser loss is not the main factor for low serum albumin in patients with CKD. Finally, hypoalbuminemia predisposes to higher morbidity and mortality only in the presence of inflammation.

Expanded Haemodialysis: Impact on Hospitalisations and Cardiovascular Events

Jernej Pajek

Pajek explained that the incidence of hospitalisation in the ESRD population is highest in patients on HD, slightly lower in those on PD, and much lower in transplant recipients.[35] The predominant single causes of hospitalisation in patients with ESRD are CV causes and infections.[35]

Pajek referred to the association between the uremic milieu and inflammation and pathways for poorer outcomes in patients on dialysis described by Stenvinkel, and specified that middle and large-middle molecules, including IL-6 and TNF-α, are associated with inflammation, adhesion molecule expression, monocyte recruitment, macrophage activation, and vascular smooth muscle cell proliferation. All these events, Pajek noted, are associated with atherosclerosis, and may be a pathway to increased CV morbidity, hospitalisations, and mortality in patients on dialysis. Furthermore, larger middle molecular weight molecules, such as retinol-binding protein 4, FGF-23, and immunoglobulin light chains, are associated with one or more signs of secondary immunodeficiency (retinol-binding protein 4 is associated with impaired polymorphonuclear leukocyte [PMNL] function; FGF-23 is associated with impaired PMNL function and leukocyte inhibition; immunoglobin light chains are associated with impaired PMNL function and infectious mortality), and represent a potential pathway in which large-middle molecules may contribute to increased incidence of infections in ESRD.[36] Pajek suggested that using MCO membranes may impact CV- and infection-related morbidity and mortality.

Pajek proposed that information on the potential impact of using MCO membranes on CV events in patients on dialysis can be gained through evaluation of intermediary outcomes, such as ACE expression, vascular calcification, and the presence of endothelial microparticles, also known as microvesicles, in the blood.

ACE expression was evaluated in a study in which blood from healthy volunteers was challenged with endotoxins, then their plasma was dialysed *in vitro*, and the effects of the plasma and dialysate on monocyte messenger RNA expression were evaluated.[37] Plasma dialysed using an MCO or high cut-off membrane was associated with lower transcript expression of ACE messenger RNA and higher expression of the ACE2 isoform in monocytes compared with that using a high-flux membrane.[37] As highlighted by Pajek, these results are relevant as a high ACE-to-ACE2 ratio is associated with an inflammatory and adhesive monocyte phenotype. The resultant dialysate using an MCO dialysis membrane caused greater induction of ACE compared with dialysate spent by dialysis with standard high-flux membrane. These results indicate that using an MCO membrane may impact on the inflammatory and adhesive phenotype of monocytes, and this may translate to reduced CV morbidity and mortality.[37]

The impact of HDx on vascular calcification was shown in a study in which serum from patients who underwent dialysis using an MCO membrane was associated with a 48% decrement in calcification of VSMCs *in vitro* compared with that from patients who underwent dialysis using a high-flux membrane.[38] Lower calcium deposition in VSMCs was also observed using serum from patients who underwent HDx compared with regular HD in a small (20 patients), randomised, crossover study.[39]

Some uremic toxins, including p-Cresol sulfate and indoxyl sulfate, may activate endothelial cells to produce microvesicles, which are associated with vascular calcification, inflammation, oxidative stress, blood coagulation, and endothelial dysfunction.[40] A study in which 63 patients on dialysis were randomised to continue with OL-HDF or switch to MCO dialysis membrane for 6 months showed a significant decrease in plasma endothelial microvesicles with MCO ($p<0.05$) compared with an increase with OL-HDF ($p<0.05$).[41]

According to Pajek, these three studies evaluating intermediary mechanisms indicate that dialysis with MCO may lead to lower CV morbidity and mortality; however, there are few hard endpoint data in this area.

A study conducted in South Korea with 80 patients randomised to HDx using the MCO membrane or OL-HDF for 1 year showed that

there was no difference between the treatment groups for all-cause survival, CV survival, left ventricular ejection fraction, left ventricular mass index, and diastolic function of the heart.[42] However, there was a slight increase in the calcium artery calcification score in the MCO membrane group.[42]

A 1 year observational study of almost 1,000 patients recruited in 2017 in Colombia compared quantitative data on mortality and hospitalisation rate with data from historical controls from the same HD network in 2014.[43,44] There was numerically lower mortality in HDx patients compared with historical HD controls (8.54/100 patient years [PY] versus 14.6/100 PY) and lower rates of hospitalisation (0.79/PY versus 1.15/PY) and duration of hospitalisation (6.91 hour days/PY versus 9.6 hour days/PY).[43,44]

Similar data on hospitalisation were reported for a single-arm observational study in Colombia, in which 81 patients were switched from dialysis with a high-flux dialysis membrane to that with an MCO membrane.[45] There was a notable decrease in the duration of hospitalisation with HDx compared with high-flux HD (4.41 versus 5.94 hospitalisation days per year; $p<0.01$).[45]

Further data on hospitalisations are available from the randomised controlled trial discussed by Stenvinkel in which 172 patients were randomised to either MCO dialyser or a high-flux dialyser.[21] In this study, there was a 52% reduction in rate ratio of hospitalisation for the MCO dialyser compared with the high-flux dialyser.[21,46] The aforementioned study of 20 patients who underwent HDx and regular HD in a randomised, crossover study[39] also showed numerically higher hospitalisation rates in the HD group ($p=0.079$).[47] This study also showed a lower infection incidence signal with HDx compared with regular HD ($p=0.03$),[47] as did a meta-analysis of the impact of the MCO membrane compared with a regular high-flux membrane.[46]

Pajek concluded that CV disease and infections are the cause of the majority of hospitalisations in dialysis patients, and that *in vitro* studies indicate HDx may offer benefits beyond contemporary HD. A randomised controlled trial of HDx versus HD/HDF evaluating CV endpoints, as well as the rates and duration of hospitalisations, is still lacking. Future research should focus on an adequately powered randomised controlled trial. Finally, reimbursement issues need to be addressed.

Improving Patient-Reported Outcomes: The Impact of Expanded Haemodialysis Therapy on Quality of Life and Symptom Burden

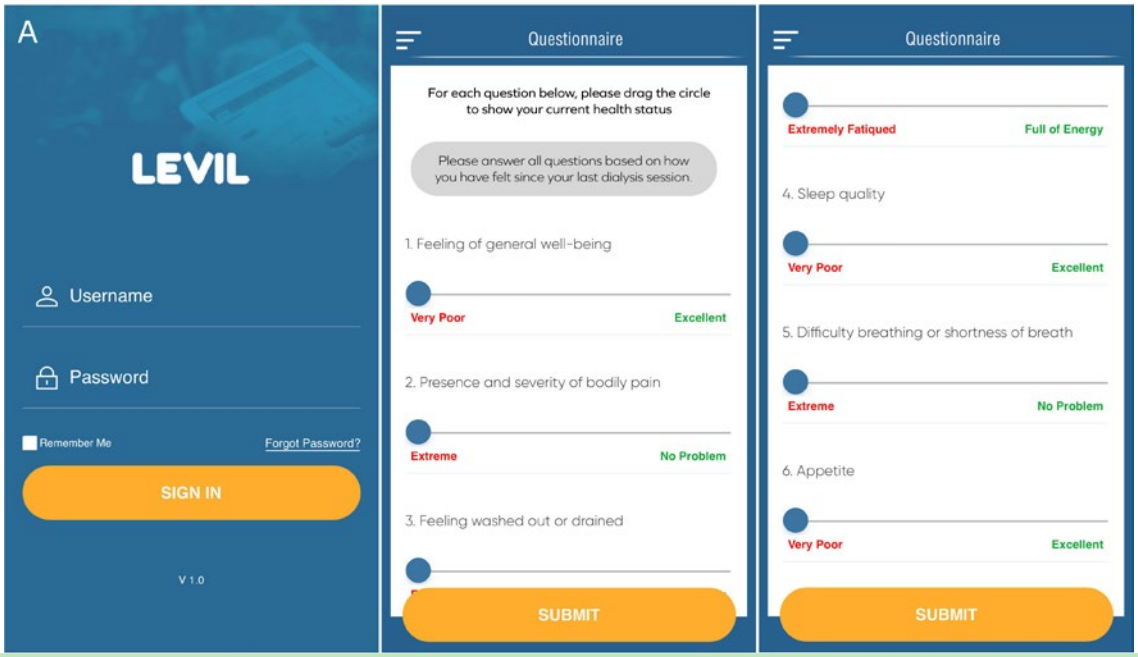
Jarrin D. Penny

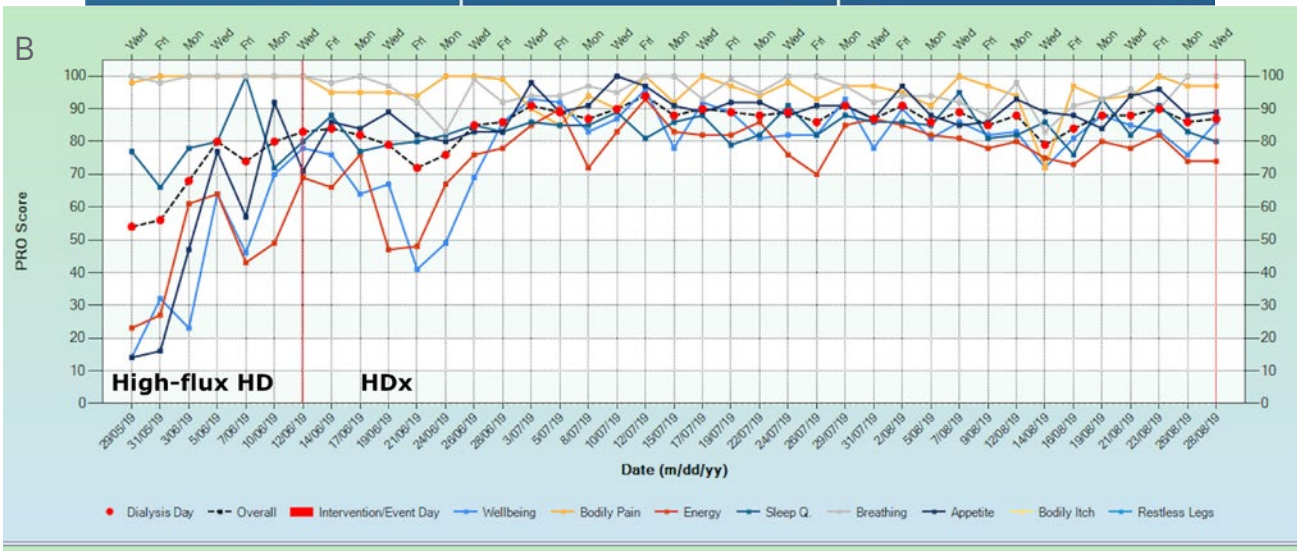
Penny began her presentation with a quote from a patient undergoing dialysis: "I understand why I need dialysis, but how can anything that makes me feel this bad not be hurting me?"

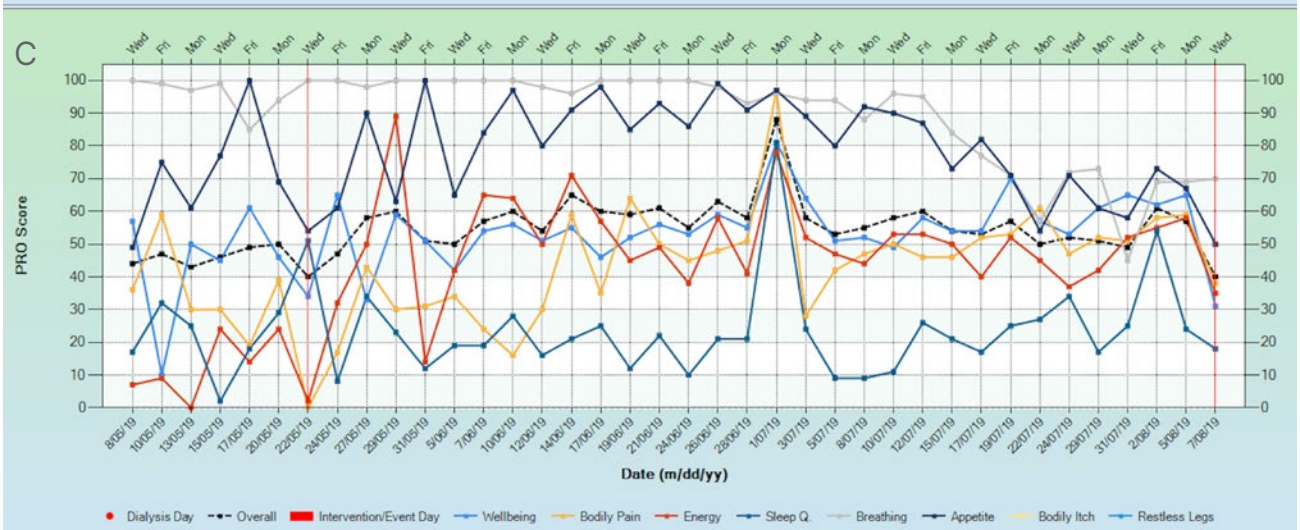
She explained that patients usually arrive for dialysis feeling generally well; however, after dialysis they feel drained and exhausted, and this provokes an important question: what are we doing to our patients? Penny recounted that many of the dialysis patients she has cared for over the last 25 years have told her that they feel their best just before they are about to undergo dialysis again, and she asked the audience to imagine living life knowing that the treatment that is keeping them alive is also making them feel unwell. Dialysis is associated with an erratic presentation of a range of symptoms that impact QoL, with no two days being the same for patients.

Penny referred to the science and compelling clinical indications associated with HDx therapy presented by Stenvinkel and Pajek, respectively, and questioned whether removing middle molecules using HDx therapy could potentially improve QoL and symptom burden in patients on dialysis. She outlined a study conducted to establish whether 12 weeks of HDx therapy had a direct impact on QoL and symptom burden measured by the London Evaluation of Illness (LEVIL) on a scale of 0 (poor) to 100 (excellent) for each of the six symptom domains (general wellbeing, energy, sleep, pain, appetite, breathing).[48] The system automatically calculated an 'overall QoL' score, which was the average of all six domains combined. Penny described LEVIL as a dynamic, easy-to-use, timely PROM tool with a visual analogue scale that can be used repeatedly for real-time tracking of

Figure 1: A) London Evaluation of Illness (LEVIL) application questions. B) Example of a patient's response to haemodialysis as LEVIL graphical output. C) Variability in symptoms day-to-day using LEVIL, for conventional high-flux haemodialysis.







symptoms and patient response to treatment. She clarified that this tool is unlike traditional QoL assessment tools, which are cross-sectional, time-consuming, and do not represent the patient's changing condition. A threshold LEVIL score of 70 was chosen by patients to distinguish between high (good) and low (bad) scoring, and this cut-off was used to stratify the data.

Penny described the study population as those who experienced low QoL and high symptom burden, tended to be on dialysis for longer, and had no residual renal output.[48] The majority of the study population suffered from poor general wellbeing, and showed a significant improvement after 8 weeks of HDx therapy ($p=0.001$). All participants had poor energy levels at baseline, which also improved after 8 weeks of HDx therapy ($p=0.001$). Sleep quality improved after approximately 4 weeks of treatment, and continued to improve throughout the study ($p=0.01$ at 4 weeks and $p<0.001$ at 12 weeks). There was also an improvement in appetite and pain with HDx therapy; however, statistical significance was not reached. There was no change in breathing. When all the symptom domains were combined to give a measure of overall QoL, the results were consistent, showing an improvement after 8 weeks of HDx therapy ($p<0.001$). The LEVIL data for the initial 2-week observation period (conventional high-flux HD) followed by 12 weeks of HDx in the study are shown in Figure 1.[48] This figure clearly shows the change in pattern of the LEVIL scores, reflecting an improvement in symptoms, after switching from high-flux HD to HDx.[48] Penny suggested that the improved QoL and symptom burden after 8 weeks of HDx therapy in this study implied a putative clearance-based effect of symptom improvement. She noted that LEVIL can help clinicians determine which patients may benefit from HDx therapy, and to assess individual response to treatment over time, which is a useful resource management tool considering the financial constraints in dialysis therapy.

Penny summarised further information that was gleaned from discussions with the study patients, who described improvements in restless leg syndrome, post-dialysis recovery time, and pruritus on HDx therapy alongside their improvement in pre-existing LEVIL domains.

Penny then discussed an index case of a haemodialysis patient with debilitating pruritus and extreme levels of tissue sodium (measured by ^{23}Na MRI). An 80-year-old male suffered from debilitating bodily itch, which meant that neither they nor their wife had slept for months; they also had raised vesicles on his shins, which added to their pruritus.[49] Numerous medications and dermatology referrals were unsuccessful, and the patient was considering discontinuing dialysis because of their poor QoL. After 12 weeks of HDx therapy (in the study), however, the itch had resolved, the vesicles healed, and the patient's (and their wife's) sleep and QoL improved.[49]

In a separate case, the participant's testimonial explained their improvement in appetite, sleep quality, and anxiety after starting HDx therapy. The patient explained the return of symptoms when they were switched back to high-flux HD, and admitted they were "really disappointed". HDx was then reinitiated and, after a couple of days, appetite, sleep, and anxiety improved again. The patient emphasised that there was "definitely a difference" between the two treatments (HDx and high-flux HD), and Penny described this case as being extremely impactful.

Penny then outlined a 60-week multicentre trial extension in Canada and the USA, which aims to enhance the understanding of the symptoms that HDx impacts and incorporates these further learnings (restless leg syndrome, pruritus, mood, recovery time) with additional focus on the impact of HDx therapy at the microcirculatory level. She expects to provide insights on the trial, with preliminary results in 2023. Penny is also interested in the impact of HDx on cognitive function and sexual dysfunction.

Penny concluded with a question for the audience: if you could change just one thing about the therapy you deliver, what would it be?

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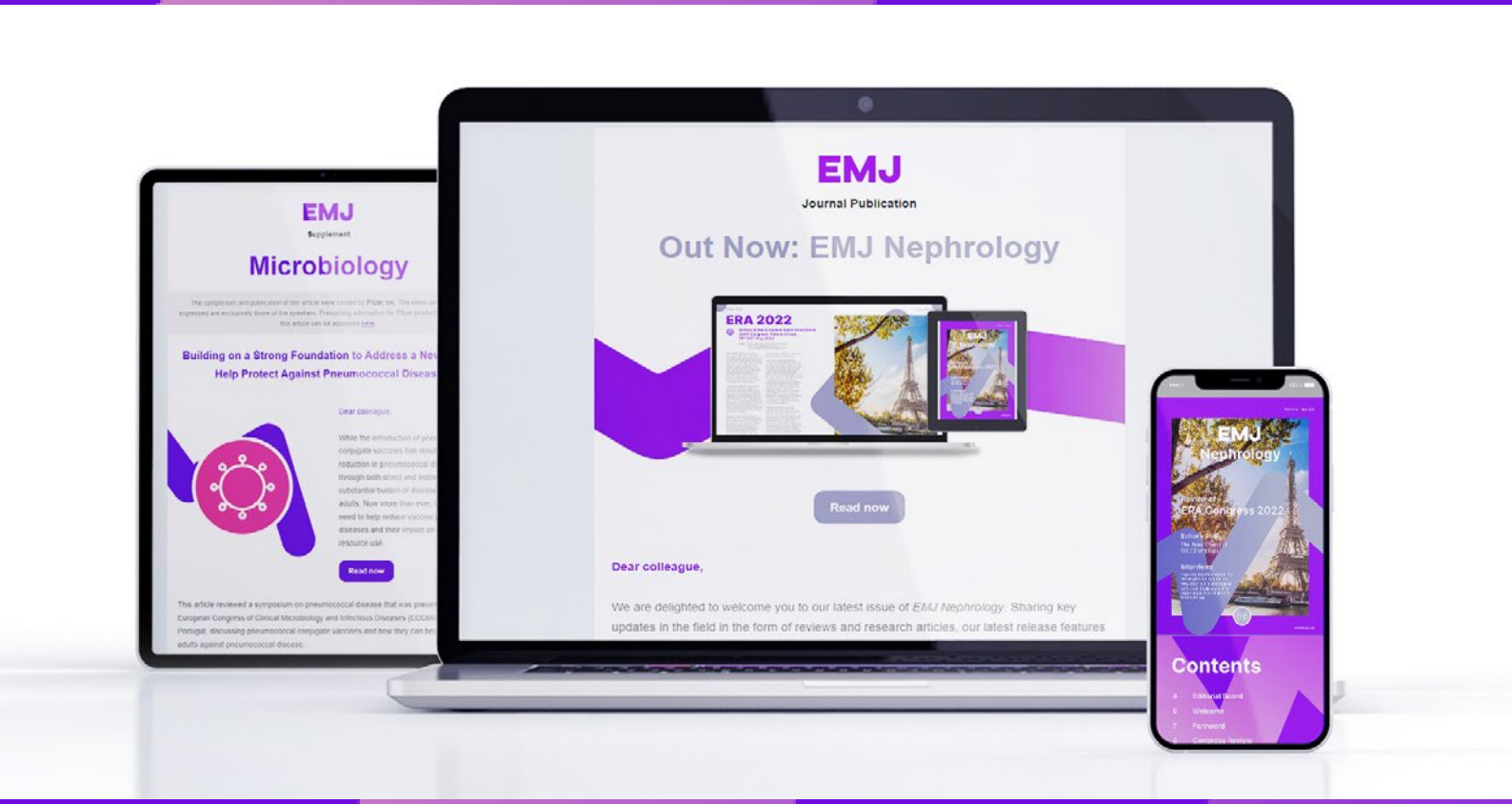

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Abstract Reviews

Introducing key insights into the latest research in nephrology, from abstracts presented at the 59th annual European Renal Association (ERA) 2022 Congress

The Association of Left Ventricular Diastolic Dysfunction and Heart Failure in Patients with Chronic Kidney Disease

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Keywords: Chronic kidney disease (CKD), heart failure (HF), left ventricular diastolic dysfunction.

Citation: EMJ Nephrol. 2022;10[1]:42-44. Abstract Review No. AR1.

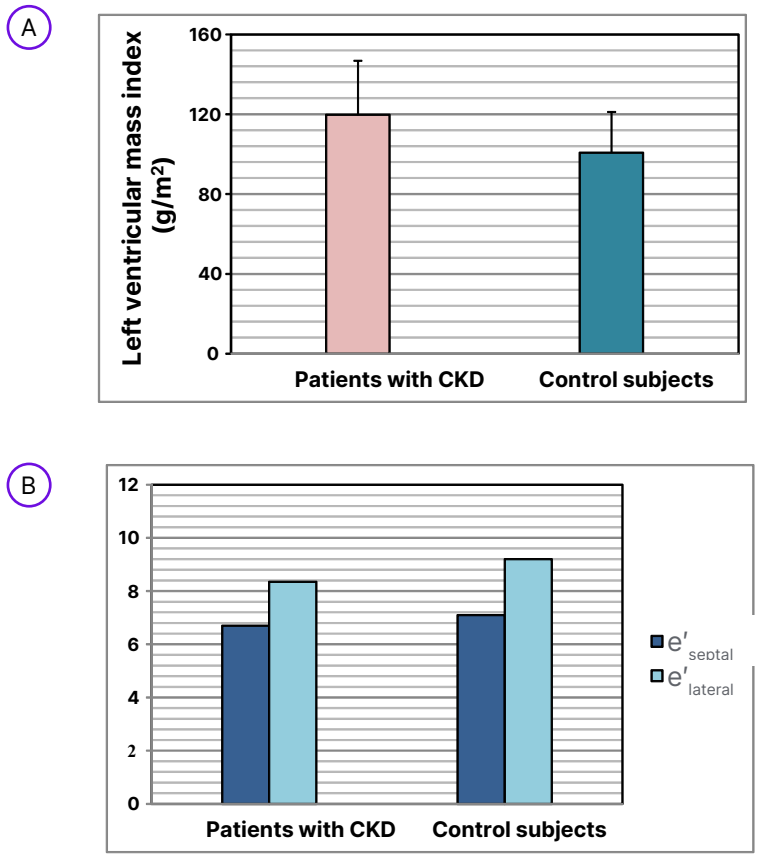
BACKGROUND AND AIMS

Chronic kidney disease (CKD) has been linked with an increased risk of cardiovascular events, especially in the dialysis population. In patients with CKD, heart function disturbances are twice as common as in the general population.[1] Heart failure (HF) is a major cause of cardiovascular mortality in patients with CKD.[2] Bearing in mind that left ventricular hypertrophy is considered to be one of the most important parameters for the occurrence of cardiovascular disease in CKD,[3] the aim of the present study was to evaluate the association of left ventricular diastolic dysfunction with HF in patients with CKD.

MATERIALS AND METHODS

The research was conducted as a prospective observational study, which included 30 patients with CKD, Stages III and IV according to Kidney Disease Improving Global Outcomes (KDIGO) staging,[4] and left ventricular diastolic dysfunction. The study also included 30 control subjects who had left ventricular diastolic

Figure 1: A) Left ventricular mass index and B) left ventricular diastolic dysfunction in patients with chronic kidney disease and control subjects.



dysfunction but without CKD. Pulse-wave (PW) Doppler echocardiography in the apical four-chamber view and tissue Doppler imaging were performed to assess left ventricular function.[5] The measurements of mitral inflow by PW Doppler covered early (E-wave) and late (A-wave) diastolic feeling velocities, peak early diastolic velocity at the septal (e'_{septal}) and lateral ($e'_{lateral}$) mitral annular sites, and E/A ratio.

RESULTS

A comparison of left ventricular function parameters between two groups of study participants indicated that left ventricular ejection fraction (0.57±0.05% versus 0.61±0.03%) was statistically reduced in patients with CKD compared to control subjects (p<0.001). Contrary, left ventricular mass index (119.8±27.0 g/m^2 versus 100.8±20.4 g/m^2; p=0.003) was significantly higher in the patients with CKD (Figure 1A). There were no significant differences in values of left ventricular end-diastolic (53.7±4.6 mm versus 54.2±3.5 mm; p=0.636) and left ventricular end-systolic (34.7±4.5 mm versus 35.7±2.3 mm; p=0.265) dimension between patients with CKD and control subjects. The mitral inflow imaging pointed to more pronounced left ventricular diastolic dysfunction in patients with CKD than in the subjects without CKD; e'_{septal} (p=0.009) and $e'_{lateral}$ (p<0.001) velocity (Figure 1B). E/A ratio showed no marked deviation between the two study groups (p=0.787). On the other hand, when the authors analysed the frequency of HF, it was noted that newly developed episodes of cardiac decompensation were more frequent in patients with CKD than in the control group (X^2=6.667; p=0.010). Regression analysis confirmed the predictive significance of left ventricular echosonographic characteristics on the occurrence of HF in patients with CKD (odds ratio [OR]: 1.56; 95% confidence interval

[CI]: 1.11–2.18; p=0.011) and for left ventricular mass index: (OR: 1.68; 95% CI: 1.01–2.80; p=0.048 for e').

CONCLUSION

HF is more common in patients with CKD than in patients with normal kidney function. There is a positive relationship between the presence of left ventricular diastolic dysfunction and the occurrence of HF in patients with CKD. ●

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Indoxyl Sulfate and Cresyl Sulfate Are Respectively Linked to Calcium Phosphate Metabolism Variables and to Cardiovascular Morbidity in Patients on Haemodialysis

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Bone metabolism, cardiovascular outcome, dialysis, indoxyl sulfate (IS), mineral metabolism, parathyroid hormone (PTH), p-Cresyl sulfate (PCS), uraemic toxins.

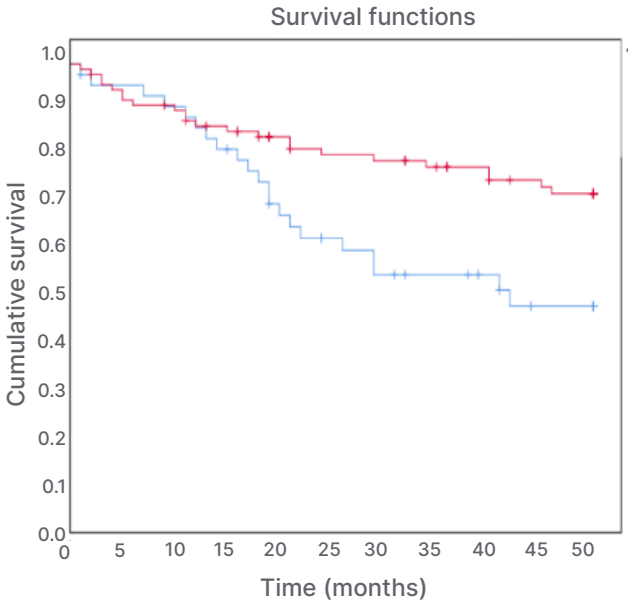
Citation: EMJ Nephrol. 2022;10[1]:44-46. Abstract Review No. AR2.

BACKGROUND AND AIMS

Indoxyl sulfate (IS) and p-Cresyl sulfate (PCS) are uraemic toxins originating from the breakdown of tryptophan and tyrosine/phenylalanine by microbiota during the intestinal fermentation of proteins.[1-3] These amino acids are respectively transformed into indole and p-Cresol and conjugated with sulfate in the liver to form IS and PCS.[3] Ninety per cent of circulating IS and CS is bound to albumin, while only 10% of their serum concentration is free and can exert toxic activities.[3-4] IS and PCS are progressively accumulated in patients with chronic kidney disease (CKD),[5-7] and were shown to promote oxidative stress and inflammation leading to tissue injury as observed in *in vitro* experiments.[8-10] The accumulation of IS and PCS was implicated in bone damage and cardiovascular disease in patients with CKD. Their cardiovascular involvement may be sustained by endothelial dysfunction, vascular calcification, and cardiac hypertrophy.[5-7]

In keeping with these findings, the authors studied the relationship between serum levels

Figure 1: Cox regression analysis evaluating cardiovascular events during a 4-year follow-up in tertiles of serum concentrations of free p-Cresyl sulfate.



of free IS and PCS with divalent ion metabolism variables and cardiovascular morbidity (stroke, heart failure, angina pectoris, and myocardial infarction) in 139 patients receiving haemodialysis (age: 68±13 years; weight: 65±13 kg; dialysis vintage: 69±71 months).

MATERIALS AND METHODS

Patients were grouped according to tertiles of serum-free IS and PCS to analyse their association with variables of mineral metabolism. Patients in the highest tertile of serum-free IS showed lower dialysis vintage and serum 1,25 hydroxyvitamin D_2 (1,25[OH]D_2) than patients in the lowest tertile (7.6±4.4 versus 11.7±9.4 pg/mL; p=0.016). They also had lower serum parathyroid hormone (PTH) than patients in the lowest tertile (180±112 versus 260±240 pg/mL; p=0.017). After this baseline determination, PTH was measured every 6 months during a 2-year follow-up. The average of these PTH values was lower in patients in the highest tertile of serum-free IS than patients in the lowest tertile (178±106 versus 254±215 pg/mL; p=0.025; 206±136 pg/mL in patients in the middle tertile). This finding was confirmed in patients not taking calcitriol during the follow-up (164±59 versus 333±383 pg/mL; p=0.05). No relationships were observed among serum-free PCS concentrations and calcium–phosphate metabolism variables.

RESULTS

During a 4-year follow-up, cardiovascular events occurred in 45 patients: 13 patients were in the lowest tertile of serum-free IS (28.9% of patients in this tertile), 16 were in the middle tertile (33.3%), and 16 were in the highest tertile (34.8%; p=0.8). Conversely, cardiovascular events were associated with tertiles of serum-free PCS as they occurred in 10 patients in the lowest tertile (20.8%), 13 in the middle (29.5%), and 22 in the highest tertile (48.8%; odds ratio: 3.3; 95% confidence interval: 1.3–8.3; p=0.01).

Cox regression analysis confirmed the increased cardiovascular morbidity in patients in the highest tertile of serum-free PCS (represented by the blue line in Figure 1) compared to those in the lowest and middle tertiles taken together (represented by the red line in Figure 1; odds ratio: 2.3; 95% confidence interval: 1.0–5.1; p=0.01). In the used model, body weight and history of cardiovascular events were also associated with cardiovascular events in the follow-up.

CONCLUSION

The authors' findings confirm the association of serum-free PCS with cardiovascular risk in patients receiving haemodialysis, as previously observed in other studies. These findings also suggest that serum-free IS was negatively related with serum PTH and 1,25(OH)D_2, suggesting that IS may have a toxic effect on parathyroid and renal cells, leading to the inhibition of PTH and 1,25(OH)D_2 release, with potential implications in the metabolic bone disease developed by patients with CKD.

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SARS-CoV-2 Infection and Kidney Impairment

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Disclosure: The authors have declared no conflicts of interest.

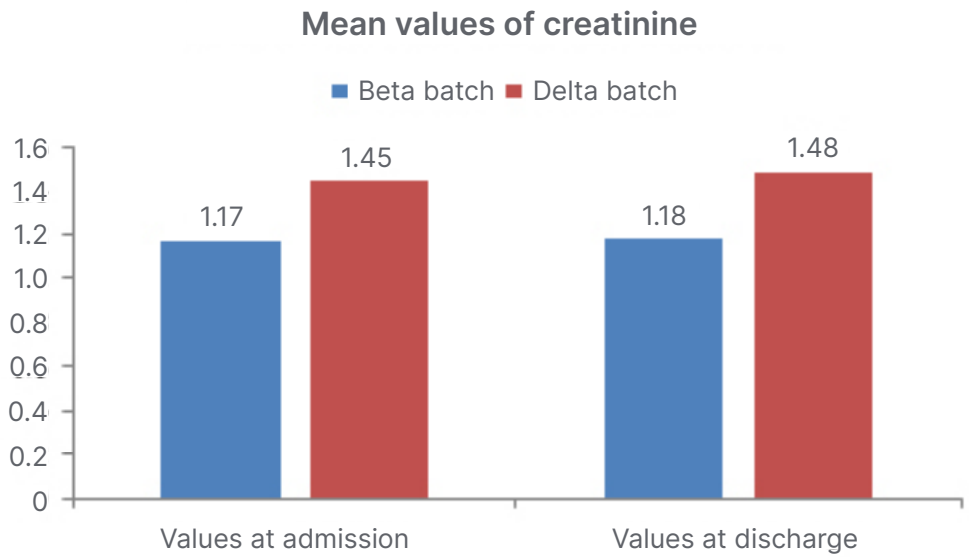
Keywords: COVID-19 infection, haemodialysis, kidney impairment, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Citation: EMJ Nephrol. 2022;10[1]:46-48. Abstract Review No. AR3.

BACKGROUND AND AIMS

The objectives of the present study are to compare the renal impairment in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) beta variant and SARS-CoV-2 delta variant in patients with or without chronic kidney disease (CKD).

Figure 1: The highlighted values of creatinine are almost equal, although a slight increase is observed within the delta batch.



MATERIALS AND METHODS

The study was performed with 80 patients from Bucharest Emergency University Hospital, Nephrology ward, Romania; 40 out of 80 patients were diagnosed with SARS-CoV-2 beta variant and 40 were diagnosed with SARS-CoV-2 delta variant. All patients' SARS-CoV-2 infections were confirmed with positive PCR tests.

In order to analyse the renal function of the patients with beta variant of SARS-CoV-2, the values of urea (mean: 55.76 mg/dL; range: 21.2–204.0 mg/dL); creatinine (mean: 1.17 mg/dL; range: 0.60–9.53 mg/dL); sodium (mean: 143.45 mmol/L; range: 135–169 mmol/L); potassium (mean: 4.506 mmol/L; range: 3.97–5.80 mmol/L); calcium (mean: 7.28 mg/dL; range: 3.5–9.09 mg/dL); phosphorus (mean: 3.16 mg/dL; range: 1.9–6.0 mg/dL); and haemoglobin (mean: 14.06 g/dL; range: 8.8–18.6 g/dL) were observed in the dynamics. Only four out of 40 patients (10%) had documented pre-existing CKD. The average period of hospitalisation was 14 days, with three (7.5%) exceptions in which patients were transferred to an intensive care unit due to the advancement of their acute respiratory failure.

In order to analyse the renal function of the patients with delta variant of SARS-COV-2, the values of urea (mean: 56.45 mg/dL; range: 22–263 mg/dL); creatinine (mean: 1.45 mg/dL; range: 0.64–5.07 mg/dL); sodium (mean: 138.85 mmol/L; range: 108–146 mmol/L); potassium (mean: 4.34 mmol/L; range: 2.3–5.07 mmol/L); calcium (mean: 8.34 mg/dL; range: 4.13–9.52 mg/dL); phosphorus (mean: 3.45 mg/dL; range: 1.9–9.7 mg/dL); and haemoglobin (mean: 14.29 g/dL; range: 11.2–15.9 g/dL) were observed in the dynamics. Only three out of 40 patients (7.5%) were diagnosed with acute kidney injury (AKI). The average period of hospitalisation was 14 days, with three exceptions (7.5%) in which patients were transferred to an intensive care unit due to the advancement of their acute respiratory failure.

RESULTS

In 36 out of 40 patients (90%) with the beta variant of SARS-CoV-2, the analysis of biological parameters showed a minimal change in their values during hospitalisation, with normal maintenance of renal function. In two patients (5%) diagnosed with CKD, an average of 3–4 haemodialysis sessions were performed with

observed improvement of renal function, while maintaining minimum nitrogen retention. In two patients with CKD (5%), renal function depreciated, leading to haemodialysis initiation.

In 33 out of 40 patients (82.5%) with the delta variant of SARS-CoV-2, the analysis of biological parameters showed minimal change in their values during hospitalisation, with normal maintenance of renal function. In four out of 40 (10.0%), the renal function depreciated in the context of multi-systems organ failure. During hospitalisation, the three patients (7.5%) who were admitted with AKI had resolved renal dysfunction by discharge.

CONCLUSION

According to this statistical analysis, the delta variant of COVID-19 does not cause kidney damage more than the beta variant of SARS-CoV-2. In the six patients (7.5%) with renal impairment, two from the beta batch (2.5%) and four from the delta batch (5%), the suspicion of renal damage in SARS-CoV-2 infection may be raised, but excluding other causes of renal damage. In the three patients (7.5%) with AKI from the delta batch, the suspicion of renal damage caused by COVID-19 may be raised, because there were no other causes for renal impairment (Figure 1).●

Course Pre-eclampsia in Patients with Advanced Chronic Kidney Disease

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Keywords: Angiogenic ratio, arterial hypertension, chronic kidney disease (CKD), pre-eclampsia (PE).

Citation: EMJ Neph. 2022;10[1]:48-49. Abstract Review No. AR4.

BACKGROUND AND AIMS

Chronic kidney disease (CKD) is a significant risk factor for pre-eclampsia (PE).[1] However, the features of PE in this cohort of patients (pts) have not been previously studied in detail.[2,3] In this regard, the analysis of PE in pts with CKD is of great clinical and social importance. The aim of the study is to analyse the incidence and characteristics of PE in pts with CKD.

MATERIALS AND METHODS

A retrospective analysis of 60 case histories of pregnant pts with CKD (Stages 1–4) was carried out, 27 of whom had CKD Stage 3a–4. Ten (37%) patients with CKD 3a–4 developed PE, then the course of their pregnancy was analysed. Creatinine level (Scr), proteinuria (PU), and blood pressure (BP) were assessed at the time of the first visit to the centre and at the time of PE. The physiological response of the kidneys to pregnancy as a decrease in Scr by 10% of the pregestational value was assessed in six pts with Scr values known before pregnancy.

Table 1: Clinical data of patients with chronic kidney disease and pre-eclampsia.

	First visit (M±SD)	PE (M±SD)
PU g/L	1.2±0.8	4.4±2.3
Scr µmol/L	157±69	224±69
SBP mmHg	131.0±11.5	142±17.0
DBP mmHg	84.0±7.3	90.0±10.6

DBP: diastolic blood pressure; M: mean; PE: pre-eclampsia; PU: proteinuria; SBP: systolic blood pressure; Scr: serum creatinine; SD: standard deviation.

RESULTS

In the group of pts with PE and advanced CKD, the mean age was 32.3 (±4.8) years (range: 28–42 years). The most common cause of CKD was glomerulonephritis (6; 60%), and one each for tubulointerstitial nephritis, diabetic nephropathy, aHUS, and APS-associated nephropathy. Four pts had CKD C3a (40%), three had C3b (30%), and three had C4 (30%). The mean term of gestation at the time of first visit to nephrologist was 15.6 weeks. At the first measurement during pregnancy, the mean Scr was 157 (±69) µmol/L; the physiological response of the kidneys to pregnancy was noted only in one out of six pts. The mean PU was 1.2 (±0.8) g/L. Three pts had arterial hypertension (30%) and only one patient received antihypertensive therapy before pregnancy with the achievement of target BP values. The mean BP values at the first visit were: SBP 131 (±11.5)/DBP 84 (±7.3) mmHg. Aspirin for the prevention of PE was prescribed in a timely manner in six cases (60%); in other cases, aspirin was either not prescribed or was added to therapy after 12 weeks of pregnancy. Of 10 pts with PE, 7 (70%) pts developed early PE (before 34 weeks of gestation); the median term for the development of PE was 31.3 weeks (27–36.5). The mean BP values at the moment of PE were 142 (±17)/90 (±10.6) mmHg. The majority of pts showed an increase in PU (Table 1). Increase in Scr was observed in six (60%) pts (Table 1). Another sign of a severe course of PE was thrombocytopaenia in two cases (<100,000 in 1 µL), in one case as the symptom of HELLP syndrome. The markers of PE (sFlt1, PLGF, sFlt1/PLGF) were analysed in 5 (50%) cases. The mean value of the ratio at the moment of PE was sFlt1/PLGF:157.6, which, for a given gestational term (31.3 weeks), corresponds to severe ischaemic damage to the placenta.

The mean delivery term was 32.4 weeks of gestation; all newborns were alive and viable with the mean weight 1,514 g (978–2,250 g).

CONCLUSION

According to study data, the incidence of PE in CKD Stages 3a–4 was 37%. The main features of PE in pts with advanced CKD were its early onset, severe course with kidney damage in 60% of cases, and relatively low BP values. ●

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Effects Of Dapagliflozin in Patients with Heart Failure

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Keywords: Dapagliflozin, ejection fraction, heart failure, sodium-glucose co-transporter inhibitor, Type 2 diabetes.

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BACKGROUND AND AIMS

In the last few years, the effectiveness and role of drugs of the sodium–glucose co-transporter inhibitor group, or the so-called gliflozins in patients with Type 2 diabetes, are being actively studied.[1-4] There are many works in the literature evaluating the effectiveness of gliflozins.[5,6] This study is dedicated to the use of sodium–glucose co-transporter inhibitors in patients with chronic heart failure.

MATERIALS AND METHODS

This study was a multi-centre prospective cohort study. The authors aimed to investigate the efficacy of dapagliflozin in patients with heart failure. Two hundred and twenty-five patients with Grade 3–4 heart failure with an ejection fraction <45% were selected. Patients received treatment with either dapagliflozin 10 mg or a placebo.

RESULTS

Initial results were received after 6 months. In the group of patients treated with dapagliflozin, a worsening of heart failure was observed in 36% fewer patients compared to the placebo group. Death from cardiovascular causes within 12 months in patients in the dapagliflozin group was observed almost two times less frequently than in patients in the placebo group.

CONCLUSION

The study's authors found that among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular events was lower among those who received dapagliflozin than among those who received the placebo, regardless of the presence or absence of diabetes. ●

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Management of Anaemia in Patients Undergoing Haemodialysis and with Minor Thalassaemia

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Keywords: Anaemia, haemodialysis, minor thalassaemia.

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BACKGROUND AND AIMS

Thalassemia is a group of haemoglobinopathies characterised by the decrease or lack of β or α globin chain production haemoglobin (Hb).[1] Minor thalassaemia has little to no symptoms since the other gene is capable of compensating for the anomaly; however, it represents a rare cause of resistance to erythropoietin (EPO) in patients with chronic haemodialysis (CHP) in multiple regions, particularly the Mediterranean region.[2] As a matter of fact, patients on CHP affected by minor thalassaemia often take higher EPO doses to correct the anaemia even if all causes of EPO resistance are resolved;[3] a recent Italian investigation indicated that EPO need in this population is almost double in comparison to other groups.[4] EPO resistance can be secondary to the quantitative anomalies of the haemoglobin chain, notably Hb A2 and Hb F. Di Lorio et al.[5] reported a positive correlation between the percentage of Hb A2 and EPO doses.[5] Patients that had a Hb A2 >6% needed higher EPO doses and vice versa. The aims of this study were to evaluate the efficiency of different therapeutic means, erythropoiesis-stimulating agents (ESA) and blood transfusion (TS), aiming to correct the anaemia in CHP with minor thalassaemia; and to detect the correlation between quantitative anomalies in Hb chains and EPO resistance.

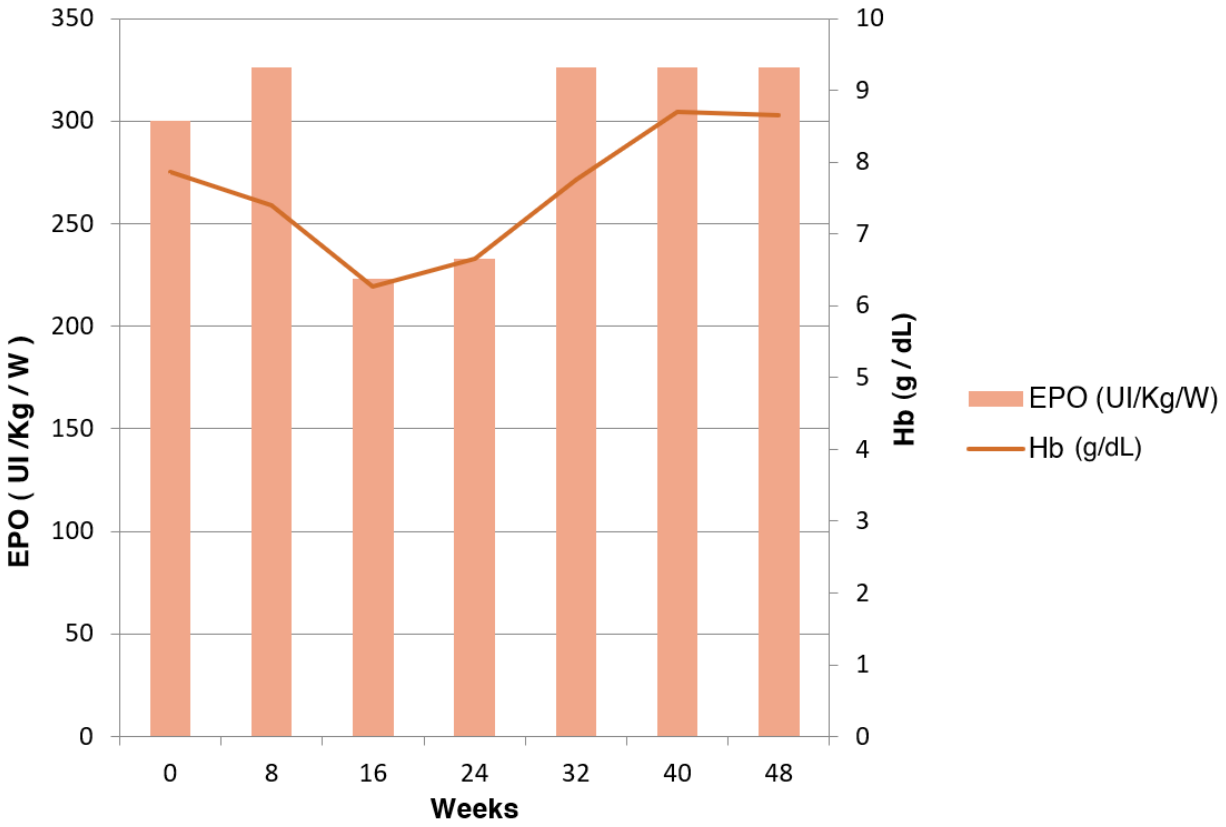
MATERIALS AND METHODS

This descriptive, multi-centre study involved eight patients on CHP affected by minor thalassaemia confirmed on electrophoresis of Hb at least 12 months prior, presenting with anaemia (Hb <10g/dL) and under-treatment by erythropoietic stimulating agents (ESA) ±transfusion, with a regular follow-up mainly of the Hb and ferritin. Statistical analysis of the data was performed through Excel using the correlation coefficient and SPSS using the p-value. A value <0.05 was considered as significant.

RESULTS

The average value of Hb was 7.35 g/dL; mean ferritin: 964±971 ng/L; and mean parathyroid hormone levels: 433±126 pg/mL. Electrophoresis was done for all patients with averages for Hb A: 96.2±1.7%; Hb A2: 3.43±1.41%; and Hb F: 0.35±0.45%. The authors noted that a decreased percentage up to null of Hb F fraction correlated with the lowest Hb levels. The main therapy in patients with anaemia was epoetin β; the average dose given to patients was 300 UI/kg/week, 326 UI/kg/week at 2 months, 233 UI/kg/week at 6 months, and 326 UI/kg/week at 12 months. Figure 1 illustrates the response to EPO during the maintenance phase. Darbepoetin α (µg/kg/s) was administered (depending on availability) to two patients out of eight. One of the two received a dose of 0.57 µg/kg/week for 8 weeks, the other one received a dose of 0.7 µg/kg/week for 8 weeks, with a different response in the two patients. Regarding TS, five patients in the series received a TS of an average of one red blood cell pellet every 3 months, given the poor clinical tolerance of the anaemia. Injectable iron was administered in two patients out of the eight ahead of the low levels of ferritin (<300 ng/L).

Figure 1: Erythropoietin doses and haemoglobin values during the maintenance phase.



EPO: erythropoietin; Hb: haemoglobin.

CONCLUSION

The presence of minor thalassaemia in CHP entails EPO resistance and a serious case of anaemia. In the authors' study, the maximum EPO dose used was 500 UI/kg/week, reaching a value of 9.7 g/dL of Hb. ●

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Congress Interviews

Ingeborg Bajema and Edwina Brown spoke with EMJ about their careers, their work for the European Renal Association (ERA), and visions for the 59th Annual ERA Congress.

Featuring: Ingeborg Bajema and Edwina Brown

ERA 2022

Ingeborg Bajema

Department of Pathology, Leiden University Medical Center, The Netherlands; Scientific Committee Member, European Renal Association; President, Renal Pathology Society, Chicago, Illinois, USA

Q1 Following your initial medical training, what led you to pursue a career in the field of nephrology and renal pathology?

During my training, I became inspired by a course in general pathology that made me feel sure that I wanted to become a pathologist. My interest in renal pathology was initiated by the people who worked in this area, in particular Jan Bruijn, who later became the promoter of my PhD thesis.

Q2 You have published over 100 peer-reviewed articles in your career. What do you believe are the current gaps in the literature?

I see many opportunities to pursue the genetic background of renal diseases that may be responsible for chronic kidney disease, where the cause sometimes remains unknown. Nephrologists, renal pathologists, and clinical geneticists should invest in this topic together. I also think there could be clues towards different inflammatory mechanisms in this area, which may have relevance for some of the histological classification systems on which I work.

Q3 You are currently a member of the scientific committee for the 59th European Renal Association (ERA) Congress. What are the most significant changes to the programme for the 2022 ERA Congress compared with last year's event?

A major change was, of course, the fact that we were so happy to have a live component to our congress again. It was great to meet others in person again. In the programme, there was a significant focus on renal pathology, which I enjoyed very much, in particular the use of artificial intelligence in our field was highlighted, which is extremely interesting.

"I think it would be great if we could create 'digital patient scenarios' in our curriculum"

Q4 The ERA have key set of values that the association adhere to. How do you think that these values translate into and impact clinical practice?

I hope they do, although we have no tools, of course, to measure whether this is truly so. In regard to the programme at the conference, I would like to compliment Annette Bruchfeld for reminding us, time and again, to keep an eye on diversity, and also on involving the young generation of scientists and physicians in the programme. I think she was very successful in doing this! In particular, recognising what young people do and rewarding them for their scientific input is one of the most important tasks we have.

"The important advice that I give my students is to be communicative: work with your colleagues, ask for advice, look up things that you are uncertain about, and get to know where you are 'unknowledgeable'"

Q5 You have always been involved in the curriculum for medical students. How do you feel the curriculum has evolved in recent years?

Because of COVID-19, a major change took place in digital teaching. It also gave an enormous impulse to the usage of digital pathology, and there are many more areas that we can explore here. I think it would be great if we could create 'digital patient scenarios' in our curriculum: digital case studies that would enable students to make clinical decisions, and where they could safely experience what happens if they make mistakes and how to correct them.

Q6 What are some points of emphasis that you incorporate into your teaching?

The important advice that I give my students is to be communicative: work with your colleagues, ask for advice, look up things that you are uncertain about, and get to know where you are 'unknowledgeable'. This is the point where you should stop and go to someone with more experience. And it is important, of course, that senior doctors should be there at that point and provide help.

Q7 What has been the proudest achievement of your career?

I think my proudest achievement is still to come, but I am confident that it will.

Edwina Brown

Professor of Renal Medicine, Department of Immunology and Inflammation, Imperial College London; Consultant Nephrologist, Imperial College Renal and Transplant Centre, Hammersmith Hospital, London, UK

Q1 Following your medical education, what sparked your interest in nephrology in particular?

Pure chance. When I qualified in 1973, no women from my group at medical school were given jobs, and we were told to look elsewhere. My first post was at a district hospital with a newly appointed general physician who was also a nephrologist. My job as his 'houseman' was to take out the rigid peritoneal dialysis catheter at the end of 48 hours of inpatient exchanges (done manually by nurses) and replace this with a plastic rod, called a Dean's prosthesis. I would then do the reverse when the person returned the next week. This continued until a haemodialysis space could be found. By the end of the job, I was putting in peritoneal dialysis catheters on my own. I loved the excitement of a new specialty and the associated physiology required to manage renal failure.

Q2 What does your role as a member of the scientific committee for the European Renal Association (ERA) entail?

A few meetings a year in advance to discuss the development of the programme, suggesting sessions and speakers. These were all on Zoom, which meant that they had to be fitted around usual activities. It also meant there was no networking with colleagues, and a lot of email work between meetings. Being European, there were no time zone problems, so meetings were not at antisocial times. At the actual meeting, it entailed being very busy with talks and chairing sessions. The pleasure of attending in-person meant that one could actually meet up with others on the committee.

Q3 What are the key themes of this year's 59th ERA Congress?

From my viewpoint, the meeting had a much stronger clinical focus than many previous ones, with sessions on improving quality of dialysis delivery pertinent to both peritoneal and haemodialysis, on delivering person-centred care with shared decision making, and expanding access to home dialysis. There was also a drive to increase the number of younger speakers, who brought a different perspective because they talked more about their own work and projects rather than subject overviews. Being asked to be a speaker also stimulated some to carry out specific projects, which made talks much more exciting.

Q4 What are your thoughts on the hybrid format of this year's congress? Do you feel that this optimises content outreach, or is an in-person event preferable for interaction?

In-person events are definitely preferable, with much better discussion after talks. In addition, networking between sessions develops ideas, as well as enabling contacts with colleagues both professionally and socially. Also, it means meeting new people; making new links; and being able to answer questions, advise, and inspire younger colleagues. However, the hybrid format does enable those who cannot travel because of work, family, or financial commitments to attend as a delegate or speaker. The hybrid nature definitely does not work when both chairs are virtual because there is no interaction with the audience.

"I loved the excitement of a new specialty and the associated physiology required to manage renal failure"

Q5 How much of an impact do you believe that the ERA Congress has both directly on nephrologists and indirectly on patients?

The sessions at the conference had strong clinical messages and were well attended. The frequent mentioning of person-centred care, advantages of home dialysis, the benefits of shared decision-making, and updates on guidelines can only improve clinical care and benefit patients. There was also plenty of time for discussion after talks, which enabled nephrologists to engage with the topic and take away important messages. The ERA itself increasingly engages with young nephrologists, has fellowship opportunities for those in training, and runs regular clinical webinars. So, there are plenty of learning opportunities.

"I think the development of young speakers at the conference is a great way to strengthen the kidney community because it empowers those at the start of their career to continue doing activities and develop ideas outside their usual clinical workload"

Q6 One of the ERA's goals is to 'strengthen the kidney community'. What steps is the organisation taking to achieve this?

I think the development of young speakers at the conference is a great way to strengthen the kidney community because it empowers those at the start of their career to continue doing activities and develop ideas outside their usual clinical workload. Hopefully, this will reinforce their role back at their home institution.

Q7 Are there any innovations on the horizon in the field of nephrology that you feel are particularly noteworthy?

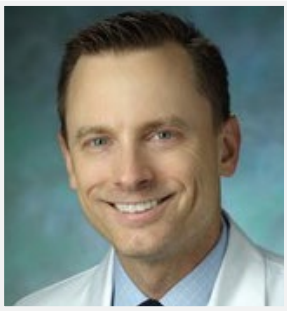
The new drugs controlling the rate of decline in diabetic and chronic kidney disease are exciting; however, we still need to learn how best to use them. We need to target them to those who are going to benefit and not as a blanket exercise, regardless of age or comorbidities.

Q8 What do you believe are the current gaps in the literature that should be addressed in the near future?

One of the big gaps is the period leading up to starting dialysis. This remains more of an art than a science, and is often at the whim of an individual nephrologist or local healthcare practice. Too many people start during a temporary decline in kidney function or without personalised decision making and are then committed to an arduous treatment, which is going to have a major impact on their day-to-day living. I suspect that the time and thought that individuals spend on choosing a new car or other major expenditure are often more than they are enabled to have when choosing dialysis and when to start.

EMJ Interviews

John Sperati and Vivek Bhalla spoke with EMJ of their careers in nephrology, the ever-changing landscape of kidney disease, and the focus of future research.



John Sperati

Director, Nephrology Fellowship Training Program; Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Q1 With over 15 years of experience working as a nephrologist, what initially led you to pursue a career in renal medicine?

A well-timed mentorship can be so influential in our career choices. The teaching and humanity I witnessed from nephrologists during medical school and residency resonated with me in a way that no other group of physicians could achieve. My grandmother was also on dialysis, so I had a meaningful family connection to the field. At its core, nephrology as a specialty offers so much more than just the delivery of dialysis for patients with end-stage kidney disease (ESKD). As a field, we became somewhat side-tracked from the science by the ESKD juggernaut, but that is changing for the better. Plus, who wouldn't be hooked by Dr McCoy curing ESKD with a pill in Star Trek IV!?

Q2 You recently published a review entitled 'Improving Primary Care Delivery for Patients Receiving Maintenance Hemodialysis'. What was the key takeaway message of this paper?

The healthcare system, in the USA in particular, is fragmented. Many patients on haemodialysis have a survival rate lower than patients with metastatic cancer. Patients interface with the healthcare system three times a week at dialysis, yet the current system is not structured to facilitate meaningful care beyond the delivery of dialysis. There is a world of opportunity here to improve patients' lives and hopefully save resources, and we need significant change in our care delivery models to do that.

Q3 You are currently the Director of the Johns Hopkins University School of Medicine (JHUSOM) Nephrology Fellowship Training Program, Baltimore, Maryland, USA. Could you tell us a bit about what this role entails and the changes that you have brought into effect since your appointment?

As the Fellowship Director, I administer and develop the training programme for our 12–14 fellows (12 clinical fellows plus one or two in dedicated research years). This entails significant administrative work around accreditation, but the joy comes from curriculum design, didactic and bedside teaching, mentoring, and hopefully inspiring the next generation

of nephrologists. Since taking the role in 2019, we have brought all curricular resources online with instant access through an app; implemented a formal Clinician Educator training pathway; launched collaborations for additional training in bioinnovation and design, global health, and critical care in nephrology; installed advanced urine microscopy equipment; and instituted a formal mentoring/advising programme. In that short time, we have had three fellows named on committees for the American Society of Nephrology (ASN), one to the National Kidney Foundation (NKF) Spring Clinical Meeting planning committee, and several to other national or international training experiences

Q4 You have a key interest in thrombotic microangiopathies involving the complement system. Could you tell us about the stage that this research is currently in?

As a college and medical student, I worked in the laboratory of Greg Stahl at Brigham & Women's Hospital, Boston, Massachusetts, USA, studying the role of complement in ischaemia reperfusion injury. This was long before the clinical introduction of complement therapeutics and the complement system was undertaught in medical schools.

With the introduction of complement therapeutics, I was able to bring

"Many patients on haemodialysis have a survival rate lower than patients with metastatic cancer"

together my interest in complement with genetics and kidney disease. I established an institutional Complement Associated Disease Registry, with a primary focus on thrombotic microangiopathies. In collaboration with my haematology colleagues at JHUSOM, as well as investigators at other institutions, we have been able to utilise the registry data to develop an *ex vivo* assay of terminal complement activation, as well as help define the relapse rate of atypical haemolytic uremic syndrome upon discontinuation of anti-C5 therapy. I am primarily a clinician and an educator, so I am able to leverage those talents by serving as the bridge between the clinic and the laboratory.

Q5 Over the years as a nephrologist, how have you seen the field change in terms of advancements in technology?

Without question, KidneyX (a collaboration between the US Department of Health and Human Services [HHS] and ASN) has been one of the most exciting developments in nephrology in the past 20 years. For the first time, we are seeing more significant investment in new technology development and one can reasonably hope a wearable artificial kidney may actually be on the horizon. In a very short time, machine learning algorithms and single cell RNA sequencing are showing how we can transform our understanding of physiology, drug development, diagnosis, and renal pathology analysis. At JHUSOM, we have been fortunate to collaborate these past 3 years with the Center for Bioengineering Innovation and Design in the School of Engineering (CBID [Johns Hopkins University Whiting School of Engineering, Baltimore, Maryland, USA). We have mentored yearly teams of bioengineering graduate students to identify and prototype novel device solutions for unmet needs within nephrology. It is difficult but promising work.

Q6 How has COVID-19 impacted renal medicine?

Sadly, it has been devastating to our patients on dialysis. It required significant advocacy for public health and hospital system officials to recognise and help address the unique risks this pandemic has posed to our patients. The pandemic has opened new lines of research into acute kidney injury, and it has required health systems to become nimbler and more creative in addressing resource allocation. The nephrology community had to learn quickly how to collaborate and share large datasets across multiple institutions in near-record time. Those processes can now be leveraged to facilitate solving other pressing problems in the field outside of COVID-19. At JHUSOM, among other impacts, the need for virtual conferencing was a nice motivation for us to reconnect with many of our former graduates. We now have alumni participating in didactic conferences and it feels right to rekindle connections that should not have so easily drifted apart over the years. Supporting this network will contribute to the success of our trainees, create opportunities, and facilitate new collaboration.

"For the first time, we are seeing more significant investment in new technology development and one can reasonably hope a wearable artificial kidney may actually be on the horizon"

Q7 How have you personally adapted your patient care during the pandemic?

I now have a healthy proportion of telemedicine appointments. As an aside, I have also decided to reinvigorate my attention to physical diagnosis for those in-person visits. For appointments that are appropriate for telemedicine, we can address the healthcare needs much more quickly. Like many others, I have had to personally navigate the challenges of working and raising school-age children during the pandemic. I understand the importance of time, or lack thereof. Being at an academic centre, we have a significant proportion of patients from other parts of the country. Thus, telemedicine has allowed us to provide better care for more patients than was previously possible. Nevertheless, the pandemic has further blurred the lines between work and home. Similar to many professions, while the new workflows have nice benefits, we have to ensure it does not become all consuming.

Q8 As an educator, where can we expect to see your focus lie in the coming years?

The need to be fluent in clinical genetics is already here for nephrologists, although we are not teaching it well. I hope, as a programme, we can further develop the requisite knowledge in genetic disease, technologies, and interpretation needed for practice in the modern era. Additionally, while I am likely in the minority on this, I believe 2 years for nephrology training is too short. We are focusing on strategies to equip our fellows with the skills and learning frameworks necessary to continue their education on what needs to be a steep curve for several years post-graduation.

Vivek Bhalla

Associate Professor of Medicine and Nephrology, Stanford University School of Medicine, California, USA; Principal Investigator, Bhalla Laboratory of Molecular Mechanisms of Kidney Disease, Stanford, California, USA

Q1 With over 20 years of experience as a nephrologist, what led you to specialise in diabetic kidney disease and the molecular mechanisms behind this?

The primary reason is that it's the most impactful disease that affects nephrology. When I was in training, there was only one medicine available to slow the progression of kidney disease and diabetes, and kidney disease in general. It is estimated that around half of all patients in a dialysis unit got there because of diabetes. So, I started my career doing molecular biology and the molecular biology of hypertension. But when I was starting to chart out on my own, I got very interested in molecular mechanisms of diabetic kidney disease because I thought it was an unmet need.

Q2 What was the key mission that you set out to achieve when you established the Bhalla Laboratory?

One of the main projects that we undertook was trying to understand why some people with diabetes develop kidney disease and why others don't. Diabetes affects millions of Americans and people around the world, but not everybody with diabetes gets kidney disease, eye disease, microvascular disease, or neuropathy. Only a portion get each of those complications, and about 15–30%, depending on how you ask the question, get some form of kidney disease with diabetes. As a researcher, that to me is a silver lining; that means that the majority of people with diabetes actually don't develop kidney disease, and I felt that this was

an opening to try to look at why that might be. After all, there are patients called 'Medallists' from a programme at the Joslin Diabetes Center, Boston, Massachusetts, USA. These are patients with Type 1 diabetes who have lived for several decades and have not developed the complications of diabetes. So, there are clearly people that have diabetes but don't get kidney disease. We started to ask the question: are there things in the kidney that could help to predict who gets kidney disease among patients with diabetes?

"I think that the treatment landscape has changed enormously for the better and it's really exciting"

Since I came from a molecular biology lab, the way to ask that question most effectively was to look at mouse models as there might be something genetic involved. In the mid-2000s, when I was starting my own lab, the National Institutes of Health (NIH) had convened to form the Animal Models of Diabetic Complications Consortium (AMDCC). Some of the original publications out of that group were trying to redefine what diabetic kidney disease was in different models. At that time, there had been very little progress made in the laboratory because many investigators were using different definitions of kidney disease and using different models. I'll give you an example: you can make a mouse diabetic in a variety of different ways; you can use a congenital model, you can use various genetic models of diabetes, you can use a toxin to model Type 1 diabetes, or use dietary changes to model Type 2 diabetes. So, there was a lot of heterogeneity, and the most common type of mouse models that were being used for all kinds of studies for a variety of different diseases actually didn't get very robust kidney disease at all. The consortium actually published several papers comparing different models of kidney disease in mice with the same diabetic insult, if you will, which allowed one to compare apples and apples instead of apples and oranges.

It was clear that there were certain strains of mice that are more prone to kidney disease than other strains of mice, even if they're all equally, or relatively equally, prone to diabetes. That was very interesting to me, and I began trying to understand what genes might dictate the susceptibility and resistance genes in these mice. And so, our lab has spent a considerable amount of time looking at these genes, and we started to really hone in on one in particular, simply because I felt it was more effective to dive deep into one gene than to cover a number of different genes more superficially. So, that's how we got started.

Q3 How was the Bhalla Laboratory impacted by COVID-19, and has the pandemic altered the way in which research is carried out?

Our lab has been very much affected by COVID-19; probably the most important way that it was affected is through laboratory personnel that have had very close relatives pass away from COVID. Probably second is that our lab had to completely shut down for a number of months, and could only open partially for a long time after this, which affected the laboratory enormously. We had personnel who had come from abroad to study with us, and their term was up by the time we were able to open again, so they were not able to accomplish any of what they wanted to accomplish. I had other personnel that needed to make a salary during that year, but weren't able to work, obviously because

the laboratory was shut down. So, at the end of the pandemic, we had this skewed budget left in the laboratory, where we did not have very much money for personnel, but a lot of unpaid money that was meant for laboratory reagents, supplies, and experiments. That was one of the major ways that our lab was affected.

Q4 How have you seen the treatment landscape of diabetic kidney disease change over the years that you have spent in research?

I think that the treatment landscape has changed enormously for the better and it's really exciting. I think we have to remember that, with all of these developments that have happened, particularly over the last 2–3 years, diabetic kidney disease is still not a curable condition. All of the efforts that were initially put forward for different molecular mechanisms have not actually yielded that many new targets. What has helped is that we've had a little bit of luck with diabetic kidney disease, a field in which we historically have had very poor luck. We've had a lot of perseverance around particular targets, along with a lot of help from industry to pursue those targets.

> **"Within the last 2–3 years, there have been therapies developed that work to slow down the progression of heart disease and kidney disease in tandem, for which there has been one successful trial after another"**

The partnership with cardiology was not anticipated; usually, cardiology and nephrology are at odds in terms of how to treat patients best. The therapy for heart failure usually adversely affects the kidney, and vice versa. But within the last 2–3 years, there have been therapies developed that work to slow down the progression of heart disease and kidney disease in tandem, for which there has been one successful trial after another. There are now two classes of medications, and soon there will hopefully be a third. So, it was 20 years of drought followed by a deluge of new therapies, and that's been enormously gratifying both as a researcher and as a physician. We now have many more options to treat patients than we did before, and we can do this aligned with our colleagues in cardiology, which makes things so much more collaborative and productive.

Q5 You have also researched Bartter's syndrome, a rare genetic disorder that causes kidney defects. Do you know of any new developments on the horizon that may be implemented to treat this disease?

Bartter's syndrome is interesting. I mentioned at the outset that I was doing research on molecular mechanisms in the kidney that were primarily related to the sodium transport of the distal nephron. As a researcher in sodium transport, one is keenly aware of most of the conditions, however rare or common, that affect sodium handling. Bartter's syndrome fits under that umbrella as a disease that makes the kidney less avid for sodium, and there's a lot of consequences of that. It's fairly rare, but it's a good model to understand how the normal kidney works. It's also a genetic model of a condition that we use to treat patients in cardiology and nephrology every single day.

There are 22 million people in the USA who take furosemide, which is a pharmacologic version of Bartter's syndrome. So, understanding what happens in Bartter syndrome can provide insights into understanding what happens when you take furosemide. We have tried to exploit this in the laboratory, and have had an

interesting time doing this while trying to better understand what happens to the nephron in that condition. Right now, I would say that there aren't any new therapies for Bartter's syndrome, but I think what's really important is that the study of this disease has become quite a bit easier from the human side due to the advent of clinical renal genetics, which is something that has happened completely in parallel with other things that we're talking about.

There have been a variety of very prominent studies looking at the role of genetics in renal disease over the last 5 years, and that has sparked a wave of much more affordable genetic testing. Patients who had a condition of Bartter's syndrome before were assumed to have that condition and there wasn't a confirmed genetic diagnosis that was associated with that. There now is, and, for a large majority of patients, coverage for genetic testing has improved enormously, which makes human disease much easier to detect and much easier to track and follow. Going forward, there will likely be larger scale studies of patients with these rare genetic tubulopathies in the near future.

Q6 Have you found that patients are generally receptive to the shift towards new technologies such as artificial intelligence, or have you experienced any resistance?

I have not had a lot of experience with artificial intelligence. The limited experience I've had with that as a clinician is that patients are interested to learn more, but they still favour the one-on-one human interaction, either in-clinic or in a virtual setting following the pandemic. I would say that every patient is different, but in general, they are still sceptical of the idea of artificial intelligence. If we can harness those types of technologies to make human–patient interactions more productive and efficient, then I think that it will be accepted quite broadly.

Q7 How do you use your role as a member of various institutions, including Stanford Bio-X, to positively impact the field of nephrology?

The Bio-X institution at Stanford is a partnership of scientists and engineers that are interested in collaboration. At this point, I have not been able to utilise my Bio-X affiliation as much as I would like, although I have had many discussions with different engineers about interesting topics in nephrology. I have tried to use my other affiliations with other organisations, such as the American Heart Association, to impact nephrology, primarily to increase its visibility in the world of cardiovascular disease, which I think is a much-needed effort.

Q8 Finally, as an educator, where can we expect to see your focus lie in the coming years?

As an educator, I will continue to showcase my enthusiasm for the field of nephrology, for both physiology and pathophysiology, and probably let people know that the field has changed a lot and is changing still. Compared to 5 years ago, we know much more about renal disease mechanisms; from rare diseases to common diseases, we now have many new therapies. There have been successful trials in chronic kidney disease for the last 2 years now, and many successful trials in the area of hypertension. So, we have different therapies and options for patients that we didn't have 5 or 10 years ago, and the idea that nephrology is a specialty where you have a condition that you can't do anything about, and you're waiting to place patients on dialysis, is no longer the case. We have made and can make enormous headway with our patients that we couldn't before, and debunking that myth will be a major focus, as well as highlighting how rich the field of nephrology has become.

The Ground Is Full of Pitfalls: Association of Chronic Kidney Disease, Conflict Zones, and the Quality of Healthcare in Africa

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Public health in sub-Saharan African countries is experiencing a double burden of diseases. First, for decades, these countries have been struggling against infectious diseases. Second, the demographic transition in the area is leading to a rising prevalence of non-communicable diseases (NCDs). Unfortunately, the health systems in sub-Saharan Africa are vulnerable, under-resourced, and unable to address these public health issues. Furthermore, protracted political instability and the consequent conflict zones are worsening the situation. In this short essay, the authors report their real-world experience of providing kidney care for patients with NCDs and chronic kidney disease (CKD) in Bunia, the capital city of the Ituri, a north-eastern district of the Democratic Republic of the Congo (DRC) that has been conflict-ridden for years. In conclusion, there is a lack of evidence and research regarding the heavy burden of NCDs and the appropriate healthcare policy in humanitarian settings such as conflict zones. A co-ordinated, standardised, and evidence-based approach is strongly recommended to reach affected populations in these areas.

COMMENTARY

"There is no nephrology here, there is only weapons," stated a 47-year-old Congolese patient with CKD (working as a United Nations [UN] staff member in Bunia) when she was asked by doctors whether there were any available nephrology clinics in the Ituri district.

The burden of NCDs is rising worldwide. Thus, the World Health Organization (WHO) has estimated, in a report related to global threats,

that 70% of global deaths in 2019 resulted from NCDs.[1] Furthermore, the global challenge represented by NCDs has been well recognised by both the UN Sustainable Development Goals and the WHO Global NCD Action Plan 2013–2020.[1,2] The target set for these guidelines is the reduction of premature deaths due to the main NCDs in the next decade. Nevertheless, three-quarters of NCD-related deaths might happen in low- and middle-income countries (LMICs).[1,3] Those countries would struggle with the growing challenge of NCDs in addition to both acute and infectious diseases.[3] This unprecedented and very dire situation is an evident issue for public health systems in LMICs. Countries in sub-Saharan Africa do not make an exception to the rule and are, like most LMICs, exposed to an unexpected epidemiological transition of contributors to disease burden.[4] The prevalence of NCDs has increased in this area and is responsible for rising disability-adjusted life years. Many phenomena, including urbanisation, unhealthy lifestyles, inequality, and poverty, might explain this tendency.[4]

On the other hand, sub-Saharan African countries have always suffered from two major barriers to accessible and quality healthcare. The first concern is related to health systems that are vulnerable, under-resourced, and relatively inaccessible to the population.[4] The second problem is the presence of political instability in some of those countries, with frequent state-based and no-state-based conflicts.[5]

NCDs management is very difficult and is even more complicated and challenging in armed conflict zones. One should know that NCDs profiles in such settings are never the same, and the simple 'one size fits all' approach to NCDs management does not apply in such contexts.[5,6] Humanitarian needs vary depending upon location of the conflict and demographic characteristics of the population involved in clashes. For example, obesity, diabetes, and cardiovascular diseases were the main recorded NCDs among refugees during the Syrian conflict.[7] In contrast, hypertension was the first health condition among some displaced persons in Central Africa.[5,6] Furthermore, NCDs have not always been the top priorities of health pracitioners.[8] For several reasons, communicable (infectious) diseases are always prioritised over NCDs, and rather than building an efficient health system, aid usually goes to security purposes. Lack of clear and evidence-based guidelines is an additional barrier to appropriate NCDs management in such disruptive settings.[8]

REAL-WORLD EXPERIENCE OF PROVIDING HEALTHCARE IN CONFLICT SETTINGS

The case of the DRC is emblematic. The eastern part of the country has been conflict-ridden for years.[9] The area represents 10% of the landmass and is the homeland of 15% of the whole Congolese population. Hundreds of armed groups have appeared and disappeared in unstable coalitions based on ethnic selections and driven by economic interests. These persistent clashes and fights worsen the population's living conditions in those areas, with millions of refugees and internally displaced persons.[9]

The authors served as UN health workers in Bunia, the capital city of the Ituri district, an armed conflict zone in the north of the DRC, for 8 months (July 2021–February 2022). They assessed the epidemiological distribution of NCDs while providing basic medical care to samples of the population in these areas. Knowing that the life-threatening nature of the environment requires strict respect for safety regulations, the authors organised medical action around three pillars: security, kidney care, and education.

Hundreds of patients suffer from NCDs such as diabetes, hypertension, and chronic cardiac and kidney diseases. These diseases are probably more frequent in urban areas, where security issues are less threatening than in suburban and rural zones. Unexpectedly, CKD is an important component. The underlying causes of CKD are not well identified. Unknown causes are the most common; otherwise, chronic HIV infection and NCDs, including diabetes and hypertension, are expected to cause a rise in the prevalence of CKD. Patients with CKD are poorly informed about their conditions, receive inadequate care, and frequently use traditional medicine products for their medication. The local health system is fragmented and unable to address the additional rising burden of CKD and other NCDs. Moreover, the supply of material resources and essential

drugs suffers from frequent interruptions because of logistical issues, which is a familiar obstacle in conflict settings.

Multiples cases of acute kidney injury are also diagnosed following infections (such as malaria, diarrhoea, etc.). The authors noticed no indication of renal replacement therapy in all cases of reported kidney failure. Nevertheless, the authors selected peritoneal dialysis as the renal replacement therapy technique given the context (frequent lack of electricity). Although the required materials (peritoneal dialysis solutions and catheters) were not available, the authors collaborated with the local authorities and secured the commitment to facilitate access to these materials.

The enhancement of population awareness against NCDs was also an important target. Thus, the authors established a training programme in co-ordination with the International Committee of the Red Cross (ICRC). The training objectives were the basic medical management of acute infectious diseases and main NCDs. Approximately 30 Congolese youths were trained in the diagnosis, basic primary care, and follow-up of chronic conditions, including hypertension, diabetes, and CKD. The learners were also initiated to the organisation of follow-up care, the use of some medical devices (blood pressure measurement, capillary blood glucose testing, etc.), interpretation of laboratory tests, and patient information. Training tools also included clinical practice and simulations.

During recent years, some medical facilities in the city of Bunia have dedicated their activities to the care and prevention of NCDs; received medical specialists from abroad; and developed, through the transfer of knowledge, a degree of expertise in NCDs management.

CONCLUDING REMARKS

Some sub-Saharan African regions and countries are affected by protracted and multiple conflicts.[3,10] In 2015, the average duration of a refugee's displacement reached 26 years, leading to increased prevalence of NCDs among those vulnerable populations.[3] While becoming long-lasting, such clashes are adding tremendous obstacles to the traditional healthcare barriers, transforming people involved in such conflicts into hostages. This not only exacerbates inequities in access to care but also adversely impacts the quality of CKD management received by patients.[3] Several reports have shown that healthcare interventions in such areas are complicated and impacted by multiple factors. Aebischer Perone et al.[11] presented 10 fundamental questions that every humanitarian actor should consider before providing care for NCDs in emergency settings. Although telehealth could offer an alternative solution in such settings, there is lack of research regarding the usefulness of this approach in crisis.[11,12]

Unfortunately, the public–private partnership is very weak. In order to address the complicated issue of care for NCDs in conflict settings, the authors advocate for healthcare actors to work in a co-ordinated fashion. The available human and financial resources were limited. Nevertheless, the authors contributed to providing basic healthcare to hundreds of patients with NCDs as well as dozens of individuals with CKD. The authors also participated vigorously to enhance awareness of CKD and acute kidney injury in the conflict-affected setting. Although the authors consider their efforts insufficient, they nourish the hope that more structured, co-ordinated, and efficient interventions will be organised in the future.[5-12]

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Focal Segmental Glomerulosclerosis: Histopathology Discussion

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INTRODUCTION

In focal segmental glomerulosclerosis (FSGS), some (not all) glomeruli are affected with sclerosis (focal), and each diseased glomerulus is only partially affected (segmental).[1-3] Sclerosis means renal vasculature is affected in a way similar to arteriosclerosis. Specifically, there occurs stiffness and obstruction in the vessels.[2,3] Initially, juxtamedullary area is affected with sclerosis.[3] As the disease advances, there is accumulation of glomerular collagen (Type IV).[2] This proteinaceous material appears glassy pink on haematoxylin and eosin stain, and is called hyalinosis.[3] FSGS is classified into primary FSGS, secondary FSGS, genetic FSGS, and FSGS of undetermined cause (FSGS-UC).[4] If kidney biopsy reveals FSGS lesions, and patient has nephrotic syndrome (24 hours proteinuria >3.5 g and presence of serum albumin <30 g/L, with or without oedema), then there is more probability of primary FSGS.[4] This is especially true if the electron microscopy shows diffuse foot process effacement.[4] If the patient does not satisfy this criterion, then they should be investigated for secondary FSGS.[4] Secondary FSGS could occur due to diabetic nephropathy, hypertensive nephrosclerosis, obesity, viral infections (including severe acute respiratory syndrome coronavirus 2, HIV, cytomegalovirus, Epstein–Barr virus, Hepatitis C virus, and Parvovirus B19), drug induced (including due to nonsteroidal anti-inflammatory drugs, steroids, calcineurin inhibitors, mammalian target of rapamycin inhibitors, and lithium), and reduced nephron number (as in sickle cell disease, age -related FSGS, renal dysplasia, and reflux nephropathy).[1,4] Genetic testing to exclude

genetic forms of FSGS (mutations in podocyte and glomerular basement membrane proteins) may be needed when subject does not meet the criteria for primary FSGS.[4] In this paper, the authors present a histopathological discussion on FSGS.

DISCUSSION

Kidney Disease: Improving Global Outcomes (KDIGO) has recently recommended following clinical-pathologic or aetiologic classification of FSGS.[4]

Primary FSGS

KDIGO has recommended that when a patient has nephrotic syndrome, and in kidney biopsy, the light microscopy shows focal and segmental glomerulosclerosis lesions, and the electron microscopy shows diffuse foot process effacement, then it satisfies the recommended definition of primary FSGS.[4] However, please note that no histopathological finding is pathognomonic of primary FSGS. Nephrotic syndrome is defined as 24-hour proteinuria of greater than 3.5 g, plus hypoalbuminaemia of less than 30 g/L, often with or without dyslipidaemia and oedema.[4] There should not be any established pathophysiologic entity that may cause FSGS (no secondary factors that can cause FSGS should have been identified).[4]

Secondary FSGS

When a patient has FSGS lesions in presence of secondary factors that are known to cause FSGS, then it is termed as secondary FSGS. Electron microscopy may or may not show diffuse foot process effacement.[4] Secondary causes of FSGS include, but are not limited to, diabetic nephropathy, hypertensive nephrosclerosis, obesity, viral infections (including severe acute respiratory syndrome coronavirus 2, HIV, and Hepatitis C), drug induced (including due to nonsteroidal anti-inflammatory drugs, steroids, calcineurin inhibitors, mammalian target of rapamycin inhibitors, heroin, interferon-α, and pamidronate), and reduced nephron number (as in age-related FSGS, renal dysplasia, surgical ablation, and reflux nephropathy).[1,2,4]

Genetic FSGS

Mutations in podocyte or glomerular basement membrane proteins may result in genetic FSGS.[4] The mutations may occur in proteins including podocin, nephrin, α-actinin-4, and β-integrin.[3] Patients with genetic forms of FSGS may have a family history of kidney disease, and they are often young.[4]

FSGS of Undetermined Cause

When no secondary cause of FSGS is identified, there is no identifiable genetic cause, nephrotic syndrome is not present, and electron microscopy does not reveal diffuse foot process effacement, then this type of FSGS is termed as FSGS-UC.[4]

HISTOPATHOLOGIC FINDINGS IN FSGS

Please refer to Figures 1–3 in this paper that showcase the FSGS histopathology.

Figure 1A shows three glomeruli. Among the three glomeruli, one of them shows segmental sclerosis and adhesion (periodic acid–Schiff [PAS] stain, x10 magnification). Figure 1B shows segmental sclerosis in glomerular tuft. The sclerosis involves less than 25% of the overall area. There is synechiae formation at the tip region (PAS, x40 magnification). Figure 1C shows sclerosis in glomerular tuft with obliteration of capillary lumen due to foamy histiocytes (periodic Schiff-methenamine silver, x40 magnification).

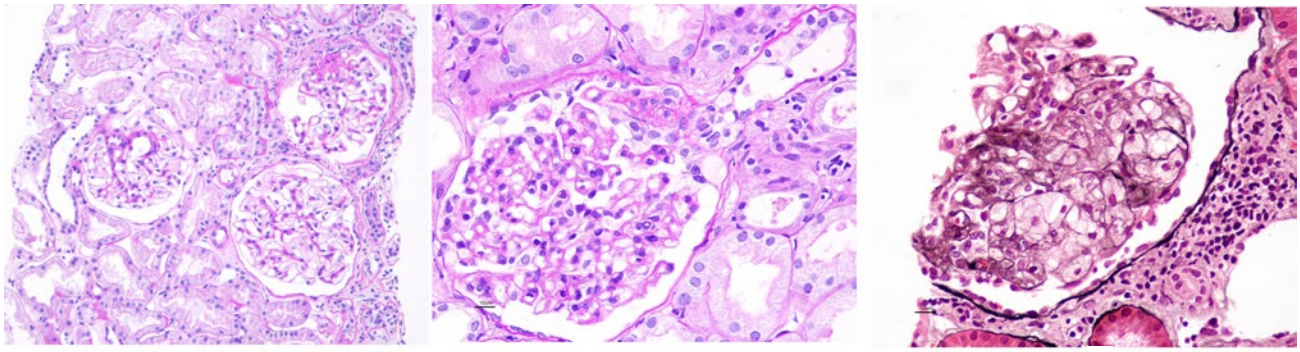
Figure 2A shows glomerulus with reactive and hyperplastic podocytes with collapse of underlying capillary tufts (Masson's trichrome, x40 magnification]. Figure 2B shows segmental hyalinosis/sclerosis in the perihilar region. Masson's trichrome stains bluish color in the solidified area (x40 magnification).

Figure 3 shows glomerular tufts with negative staining with a panel of antisera. This image is with IgG antisera (x40 magnification).

Light Microscopy

- Focal glomerulosclerosis (only some glomeruli are affected) and segmental glomerulosclerosis (only a part of a glomerulus is affected). The sclerosing segments are positive with PAS

Figure 1: Focal segmental glomerulosclerosis histopathology (periodic acid–Schiff stain)



A B C

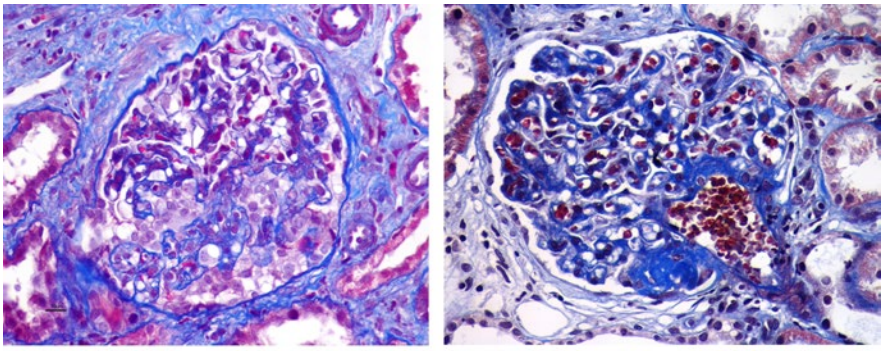
A) Among the three glomeruli, one of them shows segmental sclerosis and adhesion (PAS, x10).

B) Glomerular tuft shows segmental sclerosis involving less than 25% of the overall area, and synechiae formation at the tip region (PAS, x40).

C) Glomerular tuft shows sclerosis with obliteration of capillary lumen due to foamy histiocytes (PASM, x40).

PAS: periodic acid–Schiff stain; PASM: periodic Schiff-methenamine silver.

Figure 2: Focal segmental glomerulosclerosis histopathology (Masson's trichrome stain)



A B

A. Glomerulus revealing reactive and hyperplastic podocytes with collapse of underlying capillary tufts (MT, x40).

B. Segmental hyalinosis/sclerosis is evident in the perihilar region. MT stains bluish color in the solidified area (MT, x40).

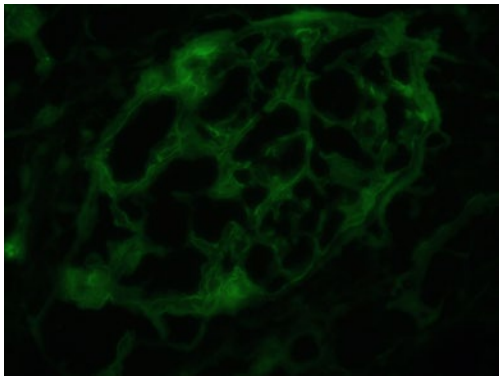
MT: Masson's trichrome.

and silver-methenamine stains that stain Type IV collagen.[1,2]

- As immunologic mechanism is not fundamental to pathogenesis of FSGS. Cell proliferation is not a characteristic feature in FSGS. Mesangial cell proliferation was believed to be a feature of FSGS in the past, and could be confused with other diseases, including IgA nephropathy coexisting with FSGS.[1-3]

- Mesangial sclerosis that appears to begin in corticomedullary region.[1-3]

Figure 3: Glomerular tufts reveals negative staining with panel of antisera.



This image is with IgG antisera (x40).

- Hyaline deposits below glomerular basement membrane.[1,2]
- Endocapillary foam cells or lipoid droplets.[1,2]
- Tubular atrophy, interstitial fibrosis, and hyaline thickening of afferent arterioles (focal lesions).[1,2]

Immunofluorescence

Because FSGS is non-immunologic in pathogenicity, immune deposits are not a characteristic feature. However, the sclerotic areas may show focal and segmental deposits of IgM and C3, particularly where hyaline material is deposited.[1,3]

Electron Microscopy

- Detachment of podocytes from glomerular capillary basement membrane. The space thus created between podocytes and the basement membrane is filled with collagen, giving rise to an appearance of a halo, like halo of the moon. This halo stains paler blue (when compared with the vessels) in trichrome stain.[1,3]
- Extensive foot process effacement, even in non-sclerotic glomeruli.[1,3] In primary FSGS, podocyte foot process effacement is more severe, typically involving >80% of the basement membrane's surface area. The effacement in secondary FSGS is more uneven and patchy.[5]
- Wrinkled basement membrane.[1,3]
- Foamy macrophages.[1,3]
- Intracytoplasmic vacuoles may form in podocytes.[1,3]
- Proliferation of podocytes may occur.[1-3]
- Mesangial sclerosis with increased mesangial matrix.[1,3]
- Collapsed glomerular loops.[1,3]

Please note that sometimes in patients with FSGS, needle biopsy may sample a renal tissue that does not have FSGS lesions. In that case, FSGS diagnosis may be missed. The lesions picked up may instead suggest minimal change in disease.

HISTOLOGIC CLASSIFICATION OF FSGS, OR COLUMBIA CLASSIFICATION

FSGS Not Otherwise Specified

This is the most common form. This is a diagnosis of exclusion; this means the other variants (perihilar, cellular, tip, and collapsing) must be excluded before coining the term FSGS not otherwise specified to these lesions.[2,3] In this variant, we see focal and segmental lesions with increased extracellular matrix, and obliteration of the glomerular capillary lumen.[2,3]

FSGS Perihilar Variant

Before diagnosing FSGS lesions as perihilar variant, one must exclude hypercellular and collapsing variants. If there are some perihilar variant lesions, but even one hypercellular or collapsing variant lesion, then this is not called a perihilar variant, but a hypercellular or collapsing variant, respectively.[2] Presence of tip variant does not exclude perihilar variant. Perihilar variant is more commonly seen in secondary FSGS.[3] The requirements to diagnose perihilar variant are:

- There should be at least one glomerulus with perihilar hyalinosis, with or without sclerosis;[2,3] and
- Perihilar sclerosis and/or hyalinosis must be present in more than 50% of the glomeruli with segmental lesions.[2,3]

FSGS Cellular Variant

The tip and the collapsing variants must be excluded before the diagnosis of FSGS as cellular variant.[2] To diagnose this cellular variant, there must be at least one glomerulus with endocapillary hypercellularity, including endothelial cells, macrophages, and foam cells.[2] Foam cells are vascular endothelial cells or monocytes, and are laden with lipids.[3] This endocapillary hypercellularity must involve at least 25% of the tuft and cause occlusion of the capillary lumen.[2]

FSGS Tip Variant

The tip refers to zone of the glomerular tuft adjacent to the proximal tubule.[2,3] To diagnose the tip variant, one must exclude the collapsing variant.[2,3] This means that even if one glomerulus has a collapsing variant lesion, one cannot diagnose this FSGS as tip variant.[2] To call FSGS tip variant, at least one segmental lesion involving the tip domain must be present, with one of the following findings at the tubular lumen or neck:[2]

- Adhesion between Bowman's capsule and the tuft.[2]
- Confluence of podocytes with parietal or tubular epithelial cells.[2]

FSGS tip variant has a favorable prognosis when compared with other variants.[3]

FSGS Collapsing Variant or Collapsing Glomerulopathy

If there is any lesion with characteristics of collapsing variant, the diagnosis of all other variants is excluded. In the collapsing variant, there must be at least one glomerulus with collapse and hypertrophy and hyperplasia of overlying podocyte.[2] There may be retraction and collapse of the capillary walls.[3] Hyperplasia of podocytes is associated with this variant.[2,3] Severe proliferation of podocytes may be confused with crescent formation.[3]

SIGNIFICANCE OF THE PATHOLOGY FINDINGS IN TERMS OF THE RECOMMENDED TREATMENT

FSGS-UC and Secondary FSGS: KDIGO 2021 guidelines recommend that immunosuppressive medications should not be used to treat FSGS-UC and secondary FSGS, as there is lack of evidence to suggest any benefit of immunosuppression in this subclass of patients. Since risks outweigh benefits, the use of immunosuppressive medications in these patients should better be avoided.[1] General measures to reduce proteinuria include medications for renin–angiotensin system blockade (including, but not limited to, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), optimal control of blood pressure, salt restriction, normalising weight, stopping smoking, and exercising regularly.[1]

Treatment of primary medical condition responsible for secondary FSGS is recommended in KDIGO 2021 guidelines.[1]

Primary FSGS

KDIGO guidelines recommend high-dose oral glucocorticoids as first-line immunosuppressive therapy in primary FSGS.[1] Cyclosporin or tacrolimus are recommended in steroid-resistant primary FSGS.[1]

Histopathologic classification of FSGS helps in prognostic terms.[5] The collapsing variant has worse prognosis, with approximately 70% of patients with this variant progressing to Stage 5 chronic kidney disease.[5] Such progression in tip lesion, FSGS not otherwise specified (classic),

perihilar, and cellular variants is less common, with 5–20%, 30–40%, 30–50%, and around 30% of patients progressing to Stage 5 chronic kidney disease, respectively.[5]

KEY LEARNING POINTS

1. Light Microscopy: in FSGS, there is focal glomerulosclerosis (only some glomeruli are affected) and segmental glomerulosclerosis (only a part of a glomerulus is affected). The sclerosing segments are positive with PAS and silver-methenamine stains that stain Type IV collagen.[1,2]

2. Immunofluorescence: FSGS is non-immunologic in pathogenicity. Immune deposits are not a characteristic feature. However, the sclerotic areas may show focal and segmental deposits of IgM and C3, particularly where hyaline material is deposited.[1,3]

3. Electron microscopy is an important tool to differentiate primary and secondary FSGS. Podocyte foot process effacement is more severe in primary FSGS, generally involving >80% of the basement membrane's surface area. Secondary FSGS effacement is more uneven and patchy.[5]

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The Renal Effects of SGLT2 Inhibitors

Editor's Pick

The use of SGLT2 inhibitors for treatment beyond diabetic kidney disease and their organs protective benefits are explored recently. This review by Sawaf et al. discusses important biochemical evidence for the use of SGLT2 inhibitors for the management of chronic kidney disease and other kidney benefits. Shedding light on key clinical trials and guidelines, the authors present timely review that could aid the expanding use of this treatment in patients with various kidney diseases.

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Abstract

Sodium–glucose co-transporter inhibitors (SGLT2i) have recently gained a lot of emphasis in their role in preventing progression of chronic kidney disease and helping with cardiac mortality. Various studies have proven the benefit of these medications in the management of patients with kidney and heart disease. SGLT2i exert their effect in the proximal convoluted tubule with various downstream effects noted in the kidney also. With spreading use of these medications, it is imperative to understand the effects they have on various electrolytes and the pathways involved in bringing about these changes in the kidney. Here, the authors review the current knowledge of SGLT2i with their effects on the kidney, electrolytes, and water balance.

Key Points

1. Sodium–glucose cotransporter inhibitors (SGLT2i) exert their effect in the proximal convoluted tubule, with various downstream effects, with benefits extending beyond glycosuric effects to a role in preventing progression of chronic kidney disease and help with cardiac mortality.

2. The renal benefit of SGLT2i in preventing chronic kidney disease progression likely occurs via several mechanisms, including decreased glomerular hypertension by blocking sodium reabsorption in the proximal convoluted tubule and decreased glucose resorption in the nephron.

3. The renal effects of SGLT2i can affect biochemical and water balance, including causing an overall free water loss alongside decreased uric acid and increased magnesium levels.

INTRODUCTION

Sodium–glucose co-transporters (SGLT) play an important role in glucose transport across epithelial cells. SGLT1 plays a major role in intestinal glucose absorption, while SGLT2 reabsorbs the majority of the filtered glucose in the proximal convoluted tubule (PCT).[1] In 2011, blockage of SGLT2 in the PCT showed an increase in urine glucose in healthy subjects.[2] One year later, canagliflozin was shown to improve glycaemic control in patients with Type 2 diabetes (T2D).[3]

Over the past few years, there have been numerous landmark trials supporting the utility of SGLT2 inhibitors for patients with heart failure and chronic kidney disease (CKD).[4-6] From the kidney perspective, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have been adjusted to include SGLT2 inhibitors as first line therapy along with metformin for patients with diabetic kidney disease.[7] Dapagliflozin was also recently approved by the U.S. Food and Drug Administration (FDA) for use in high progression risk CKD patients, regardless of diabetes status. As the utility of SGLT2 inhibitors becomes more prevalent, we continue learning more about their effects on the kidney, heart, electrolytes, and other biochemicals. This review will cover the current knowledge on the renal effect, and the pathophysiological mechanism of this novel class of medications.

CHRONIC KIDNEY DISEASE

The earliest of the landmark trials that showed a potential utility of SGLT2 inhibitors (SGLT2i) in CKD was the EMPA-REG trial in 2015.[4] This trial showed that treatment with SGLT2i provides kidney protection for patients with CKD. Equally far-reaching trials followed over the next few years, including CREDENCE[5] and DAPA-CKD.[6] CREDENCE demonstrated the benefit SGLT2i provide in patients with diabetic kidney disease, while DAPA-CKD showed their utility in non-diabetic proteinuric CKD. It is now well established that the beneficial effects of SGLT2i go far beyond their glucosuric effects.

Glomerular hypertension is one of the maladaptive mechanisms that can lead to progressive CKD. The impact of SGLT2i on glomerular hypertension is now an accepted mechanism that could underscore their kidney protective effects. By blocking sodium reabsorption through SGLT2 in the PCT, there is a natriuretic effect that induces tubulo-glomerular feedback, resulting in the vasoconstriction of the glomerular afferent arteriole. This leads to decreased glomerular hyperfiltration and decreased glomerular hypertension.[8]

In addition to their effect on reducing glomerular hypertension, SGLT2i also decrease the amount of glucose being reabsorbed in the nephron. This is hypothesised to exert a protective effect against matrix expansion, interstitial fibrosis, and macrophage infiltration,[9] all of which are thought to be by-products of glucose-induced oxidative stress.[10,11] SGLT2i are also believed to provide kidney protection through generating a systemic low ketone state. In what has become known as the 'Thrifty Substrate Hypothesis', SGLT2 inhibitors generate a state of mild, persistent hyperketonaemia. Ketones are then oxidised, preferentially over free fatty acids in organs such as the heart and kidney, thereby generating less reactive oxidative species and free oxygen radicals when compared to the consumption of free fatty acids.[12,13]

SODIUM

While seemingly simple, the impact of SGLT2i on sodium balance is more complicated than the increased excretion resulting from blockage of the SGLT2 receptors.

SGLT2 is a co-transporter that transports one sodium ion for each molecule of glucose. In contrast, SGLT1 transports two sodium ions per molecule of glucose.[14,15] The location of these SGLT transporters in the PCT plays a role in the net impact of SGLT2i on sodium balance. Since SGLT1 transporter is located distal in the PCT (in the S3 segment for SGLT1 versus in the S1 and S2 segments for SGLT2), the action of SGLT2i increases the delivery of glucose to the S3 segment of the PCT. This results in an increase in SGLT1 action. From a sodium standpoint, blocking the SGLT2 transporter will result in decreased SGLT2 activity which reabsorbs one sodium molecule per glucose. However, by doing so, more glucose is available to be reabsorbed through the SGLT1

receptor, with resultant two sodium molecules reabsorbed per glucose.[16]

Other than SGLT 1 and 2, there has been evidence that SGLT2i cause the inhibition of sodium–hydrogen exchanger 3 (NHE3), which exchanges one sodium ion per hydrogen molecule. SGLT2i have been shown to directly inhibit NHE in cardiac cells in animal studies.[17,18] In the renal tubular cells, SGLT2 interacts with NHE3 through the action of membrane associated protein 17,[16] which results in decreased sodium reabsorption in the PCT. Overall, there seems to be a net negative sodium balance mediated through the inhibition of both the SGLT2 transporter, as well as the decreased action of NHE3 (Figure 1).

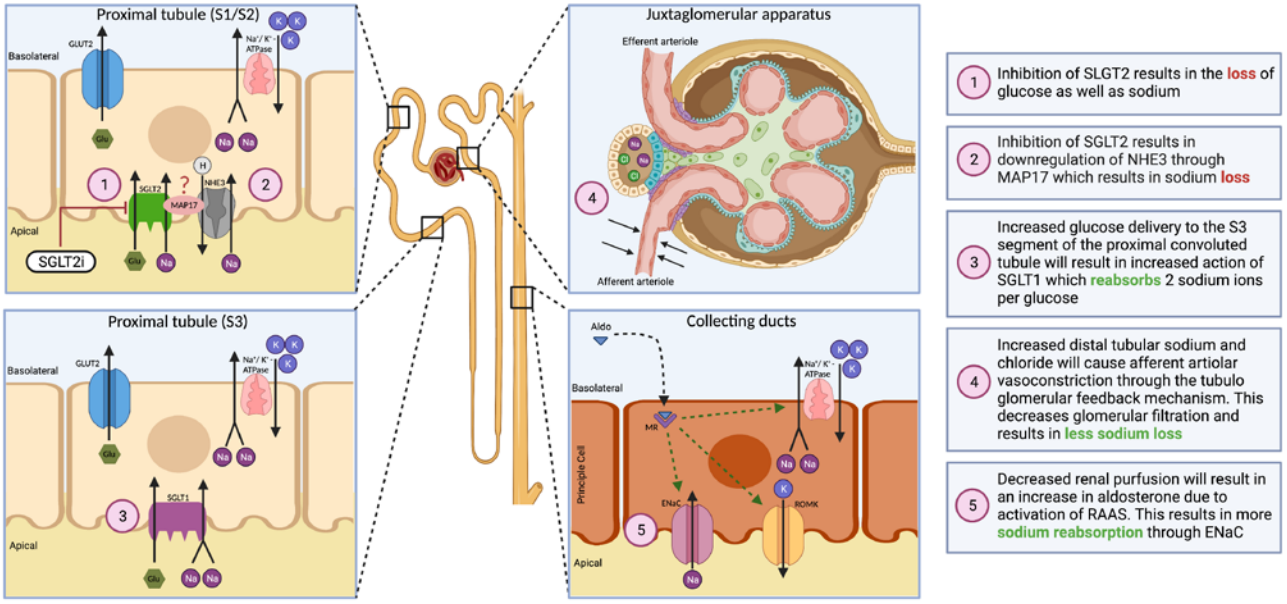
Clinically, SGLT2i have shown a measurable yet transient increase in patients' urine output and urinary sodium excretion.[19] Measurement of plasma volume to determine the overall sodium balance that occurs as a result of SGLT2i therapy showed conflicting results due to the variation in the methods of measurement. For example, when bioimpedance spectroscopy was used, there was no measurable change in total volume.[20] However, when total volume was measured using indicator dilution with I-131 albumin, a clear drop in total plasma volume was observed.[21]

Despite these mixed findings, a clear and well-established result of SLGT2i is a reduction in both systolic and diastolic blood pressures.[22-24] This change in blood pressure, albeit only mild, points towards an overall net negative sodium balance, rendering these agents effectively as weak diuretics.

MAGNESIUM

Hypomagnesaemia is an electrolyte imbalance that is observed in a large segment of patients who suffer from T2D.[25] This hypomagnesaemia has been associated with a more rapid decline of renal function,[26] higher rates of cardiovascular disease,[27,28] and is even a predictor of end-stage renal disease in these patients.[29] SGLT2i have been shown to increase serum magnesium in patients with T2D,[30] but the pathophysiology is still poorly understood.

Figure 1: Summary of sodium–glucose co-transporter 2 inhibitor effects on sodium balance.



ENaC: epithelial sodium channel; Glu: glucose; GLUT2: glucose transporter 2; K: potassium; MAP17: membrane associated protein 17; Na: sodium; NHE3: sodium hydrogen exchanger 3; RAAS: renin–angiotensin–aldosterone system; ROMK: renal outer medullary potassium channel; SGLT: sodium–glucose co-transporter; SGLT2i: sodium–glucose co-transporter 2 inhibitor.

Several mechanisms have been proposed to explain this increase in serum magnesium upon SGLT2i treatment, including haemoconcentration, resulting from the diuretic effect of SGLT2i; an increase in glucagon levels, which results in increased magnesium absorption in the distal convoluted tubules; a decrease in insulin levels, resulting in a decreased shift of magnesium intracellularly; and an increase in insulin sensitivity, which can result in an increased expression of the TRPM6 channel that further decreases magnesium urinary excretion.[25,31]

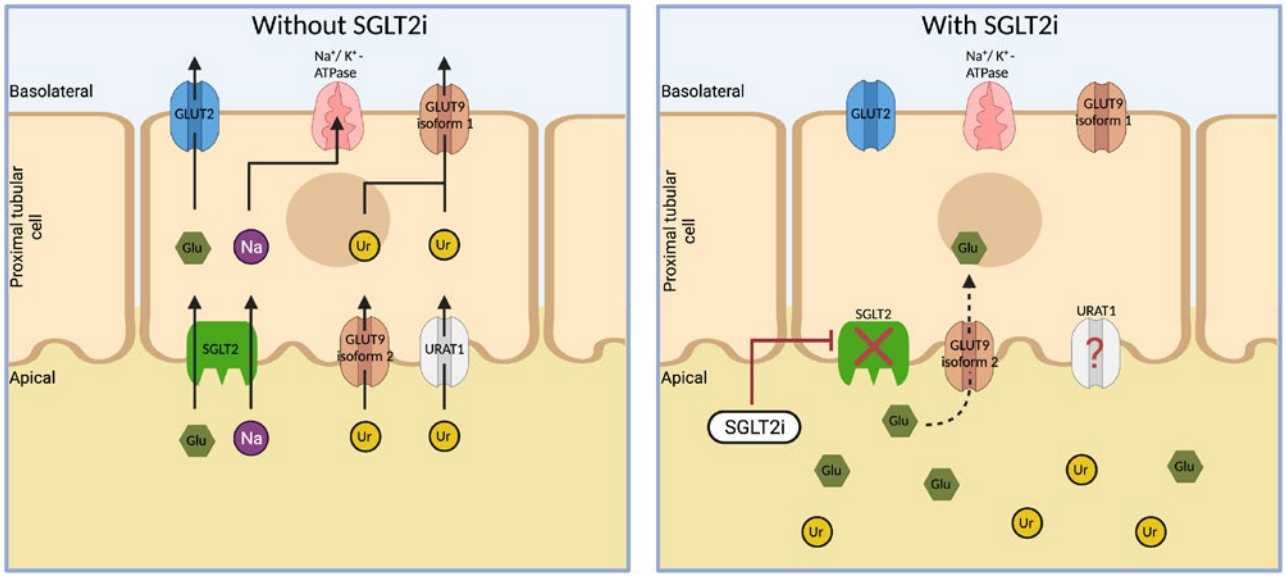
URIC ACID

Patients with T2D tend to have elevated uric acid levels which are associated with an increased risk of cardiovascular disease[32] and kidney disease. Hyperuricaemia has also been linked to faster CKD progression,[33-35] although urate-lowering therapy has not been shown to provide kidney benefits.[36,37]

SGLT2i seem to carry a urate-lowering effect beyond what would be expected as a result of the osmotic drive.[38] There is evidence that suggests that SGLT2 inhibition results in increased tubular secretion of uric acid that is mediated through glucose transporter (GLUT9) isoform 2 and urate transporter 1 (URAT1).[39] Increased urinary glucose availability with SGLT2 blockade leads to activating GLUT9 isoform 2 for glucose reabsorption as opposed to urate reabsorption, ultimately leading to a uricosuric effect. It has also been hypothesised that GLUT9 isoform 2 activation may also facilitate urate secretion.[40,41] The role of URAT1 is not well understood, but it is postulated to reabsorb urate under physiological conditions. SGLT2i downregulate URAT1, leading to more uricosuria (Figure 2).[39]

When looking at large patient analyses, there has been a considerable decrease in uric acid levels in patients receiving a SGLT2i,[42] as well as a potential protection against the incidence of gout in these patient populations.[43]

Figure 2: Visual representation of sodium–glucose co-transporters 2 inhibitor effects on urate.



The increased availability of glucose causes GLUT9 isoform 2 to reabsorb glucose rather than urate. URAT1 seems to be downregulated when SGLT2i are used; however, the mechanism behind this is not entirely clear.

Glu: glucose; GLUT9: glucose transporter 9; K: potassium; Na: sodium; SGLTi: sodium–glucose co-transporter; SGLTi: sodium–glucose co-transporter inhibitor; Ur: urate; URAT1: urate transporter 1.

PHOSPHOROUS AND CALCIUM

Phosphate levels, fibroblast growth factor 23, and parathyroid hormone have been shown to increase in patients who are on SGLT2i.[44,45] It is speculated that the increased phosphate levels are related to an increase in reabsorption through sodium phosphorous co-transporters IIa and IIc in the PCT, due to the increased abundance of sodium ions in the urinary space upon SGLT2 inhibition (Figure 3).[41]

Although there is evidence of an increase in fibroblast growth factor 23, parathyroid hormone and urinary calcium levels[44] with the use of SGLT2i, the overall effect on serum calcium levels appears minimal.[45]

WATER

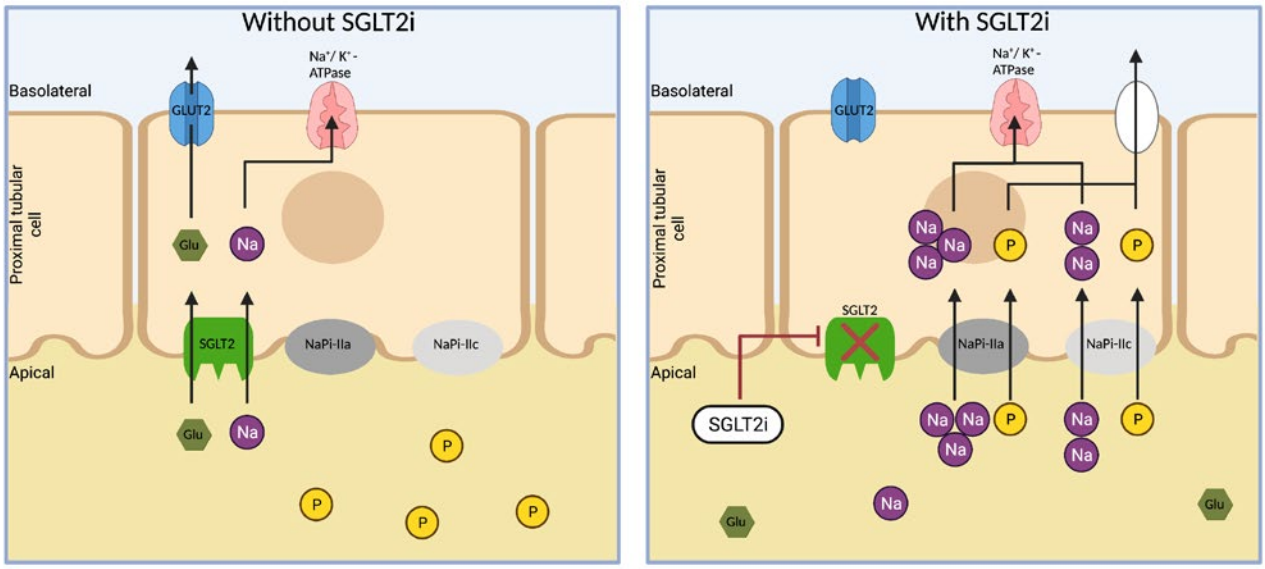
SGLT2i have an interesting effect on water balance, as they cause an increase in plasma sodium.[46] This overall free water loss is believed to occur as a result of osmotic diuresis caused by the urinary loss of glucose and sodium.[47]

This class of medications has shown a potential utility in increasing free water loss, and resulting in an increased serum sodium in patients with syndrome of inappropriate antidiuretic hormone secretion.[46] There are also ongoing investigations to determine if the SGLT2i empagliflozin can provide benefit in patients with euvolemic and hypervolemic hyponatraemia.

POTASSIUM

The effect that SGLT2i have on potassium balance is not very clear. There is some evidence that canagliflozin in particular can result in changes in potassium, but other SGLT2i do not exhibit the same effect.[48] It seems as though canagliflozin can decrease the risk of hyperkalaemia when compared with placebo in most conditions.[49] However, there have been reports of hyperkalaemia as well in specific conditions, where higher doses of canagliflozin are given in addition to renin–angiotensin–aldosterone system blockade and/or a potassium-sparing diuretic in patients with a reduced estimated glomerular filtration rate.[50] It is possible that the initial drop in

Figure 3: Visual representation of sodium–glucose co-transporter 2 inhibitors effects on phosphorous.



The increased availability of sodium will cause increased activation through NaPi IIa and IIc.

Glu: glucose; GLUT2: glucose transporter 2; Na: sodium; NaPi: sodium phosphorous co-transporters; P: phosphorous; SGLT: sodium–glucose co-transporter; SGLTi: sodium–glucose co-transporter inhibitor.

estimated glomerular filtration rate could lead to hyperkalaemia in the setting of advanced CKD; however, in the long-run, there seems to be a signal towards less hyperkalaemia.

CONCLUSION

In short, SGLT2i have revolutionised the management algorithms of CKD and heart failure. They have clear protective kidney effects in proteinuric, and possibly non-proteinuric, CKD, regardless of diabetes status or its control. Understanding of how these agents exert their protective effect is growing steadily and healthcare professionals are learning more about how they affect water and the various electrolytes. While this understanding has grown immensely in recent years, there are many questions and gaps in understanding that remain to be addressed.

SGLT2i seem to have an overall natriuretic effect, as well as an overall free water loss. They cause uric acid levels to decrease while causing magnesium levels to increase. Given the continued expansion in the use of SGLTi, it is becoming increasingly important for prescribers to realise how these revolutionary agents can contribute to different multiple facets of the patients' metabolic profiles (Table 1).

Table 1: Clinical applications of biochemical effects of sodium–glucose co-transporter inhibitors.

	Effect	Mechanism	Clinical Application
Sodium	Decrease	Inhibition of sodium absorption through SGLT2	Weak diuretic and blood pressure reducing agent. Use with caution in patients at risk of developing orthostasis or those already on diuretics
Magnesium	Increase	Decreased insulin resistance resulting in increased TRPM6 expression in DCT	Mild increase in Mg levels upon initiation of SGLT2i
Uric Acid	Decrease	Decreased tubular absorption of urate through GLUT9 isoform 2 and possibly URAT1	Agents could help decrease uric acid level in patients with hyperuricaemia
Potassium	Unclear	Unclear	SGLT2i could allow more room for renin–angiotensin–aldosterone system blockade in the long-run Given changes in either direction of potassium, it is important to check renal function panel 1–2 weeks after starting SGLT2i
Water	Decrease	Osmotic drag of free water due increased urinary sodium and glucose concentrations	Possible utility in SIADH in addition to fluid restriction

DCT: distal convoluted tubules; GLUT9: glucose transporter 9; Mg: magnesium; SGLT: sodium–glucose co-transporter; SGLTi: sodium–glucose co-transporter inhibitor; SIADH: syndrome of inappropriate antidiuretic hormone secretion; URAT1: urate transporter 1.

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COVID-19-Associated Nephropathy: An Emerging Clinical Entity

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new pathogen that was responsible for the global pandemic that started in Wuhan, China in 2019. It causes COVID-19, manifesting as viral pneumonia with concomitant acute respiratory failure and, in certain cases, multiorgan failure and death.

Kidney involvement is common and can be aetiologically heterogeneous. Acute kidney injury is mostly caused indirectly, especially in the context of systemic inflammation, hypoxaemia, hypotension, shock, and increased oxidative stress. Complement activation, tubulointerstitial damage, and endothelial dysfunction with resultant thromboses are also important factors in kidney injury. Histologically, SARS-CoV-2 was found to induce predominant tubulointerstitial changes and in some cases, glomerular changes. In a certain subgroup of patients with the *APOL1* high-risk allele variant, a collapsing glomerulopathy, similar to HIV-associated nephropathy, was found. This entity was later named COVID-19-associated nephropathy. In this article, the authors present the pathophysiology behind SARS-CoV-2-related kidney involvement and the development of COVID-19-associated nephropathy.

Key Points

1. Kidney injury in COVID-19 is common and multifactorial, occurring via several mechanisms including indirect damage in the context of systemic inflammation, hypoxaemia, hypotension, shock, and increased oxidative stress; complement activation; tubulointerstitial damage; and endothelial dysfunction with resultant thromboses.

2. A subgroup of patients with an *APOL1* high-risk allele variant have been found to have a collapsing glomerulopathy with podocyte proliferation, with or without severe acute respiratory syndrome coronavirus 2 viral inclusion particles; this entity has been named COVID-19-associated nephropathy (COVAN).

Key Points continued

3. Supportive treatment is utilised for cases of COVAN; further studies are needed to improve the recognition of these patients and to develop optimal treatment strategies.

INTRODUCTION: RECENT EPIDEMIOLOGIC DATA AND GLOBAL BURDEN OF COVID-19

In 2019, a cluster of unusual pneumonia cases was identified in Wuhan, China. The patients presented with acute respiratory distress syndrome, which resulted in respiratory failure and, in some cases, multiorgan failure and death. The disease spread throughout China and a new coronavirus, which was designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the cause of the epidemic. The resultant disease was named COVID-19, and it quickly spread worldwide, causing a global pandemic that is still currently ongoing.[1]

Since February 2022, over 350 million cases and 5.5 million deaths attributed to COVID-19 have been identified worldwide. The countries with the most confirmed cases and deaths are the USA, India, France, and Italy.[2] Due to how quickly the disease has spread, COVID-19 presents a major threat to health systems worldwide, making it one of the most prominent infectious diseases of this century.[1]

Studies have shown that COVID-19 more commonly and severely affects obese patients and those with chronic illnesses, including diabetes mellitus, arterial hypertension, and chronic kidney disease (CKD).[3] Additionally, a direct causal link between infection with SARS-CoV-2 and organ damage has been found, resulting in new pathological and clinical entities, which have thus far not been described.[4]

In this article, the authors present COVID-19-associated nephropathy (COVAN), a new variant of collapsing focal segmental glomerulosclerosis (FSGS) that has been attributed to infection with SARS-CoV-2.[4]

PATHOPHYSIOLOGY: THE EFFECTS OF SARS-COV-2 ON THE KIDNEY

Several studies and reports have shown that angiotensin-converting enzyme 2 (ACE2) is the host cell receptor for SARS-CoV-2.[5] ACE2 is an enzyme that is expressed in various human tissues, especially in the kidney, gastrointestinal tract, lungs, heart, and testes, indicating that these tissues are most susceptible to infection with the virus.[6]

ACE2 is a powerful negative regulatory peptide of the renin-angiotensin aldosterone system, as it can cause the degradation of angiotensin II and therefore lead to vasodilatation, suppression of inflammation, reduction in oxidative stress, and cell apoptosis. The infection with SARS-CoV-2 causes a downregulation of circulating ACE2 and a substantial increase in the level of angiotensin II, which is a crucial component in the cytokine storm and proinflammatory state that is often observed in patients with COVID-19.[7,8] A peptidase-independent, receptor-like function is also important in SARS-CoV-2 infection. Studies have determined that the interaction between the S1 subunit of the SARS-CoV-2 spike protein and ACE2 leads to membrane fusion between the virus and target cells, increasing the spike protein-driven viral infection. Furthermore, endocytosis may be another route by which viral entry and cell infection can take place.[9] During cellular entry, the internalisation of ACE2 leads to an increase in angiotensin II activity, thereby causing vasoconstriction, inflammation, increased oxidative stress, and cell death.[7] The kidney is one of the organs with the highest ACE2 expression and activity, especially in the podocytes, mesangial cells, and proximal tubular cells, making it extremely susceptible to SARS-CoV-2 infection.[10]

Renal damage in patients with SARS-CoV-2 is multifactorial. Firstly, indirect injury of the

renal parenchyma is common due to systemic inflammation, hypoxaemia, hypotension, shock, and increased levels of reactive oxygen species.[11] Secondly, complement activation, tubulointerstitial damage, and endothelial dysfunction with resulting vascular thromboses also contribute to kidney injury.[11] Kidney biopsy results have shown tubulointerstitial oedema, diffuse acute proximal tubular injury with the loss of brush border, protein and pigment casts in the tubular lumen, and diffuse erythrocyte aggregation in the peritubular and glomerular capillary loops. The observed glomerular lesions have been minor, with only modest endothelial swelling and non-specific immunofluorescence staining.[12] Interestingly, podocytes showed vacuolation and detachment from the glomerular basement membrane. Some studies have later reported the presence of a severe, collapsing glomerulopathy in the kidneys of patients of African descent with SARS-CoV-2 infection, mimicking the findings that were seen in patients with HIV-associated nephropathy.[13] The term COVAN was coined, representing a specific form of collapsing FSGS in patients with COVID-19.[14]

COVID-19-ASSOCIATED NEPHROPATHY (COVAN)

Collapsing glomerulopathy is a severe, aggressive, and distinct histological variant of FSGS, characterised by segmental or global glomerular tuft collapse with hypertrophy and hyperplasia of the overlying podocytes. Tubulointerstitial involvement, including acute tubular injury, tubular dilatation, and interstitial inflammation, is also a common finding.[15,16]

Weiss et al.[16] were the first to describe collapsing glomerulopathy as a clinical and pathological entity in 1986, when they presented a case series of six Black patients with proteinuric kidney impairment and glomerular collapse following a brief period of febrile illness. The series suggested that this may have been the result of a potential infectious causative agent, although no microorganism was identified.[16] Soon after, a similar clinical and histological entity was confirmed in patients with HIV.[17]

In general, collapsing glomerulopathy can be primary or secondary in association with different clinical entities, including malignancies, thrombotic microangiopathy, sickle cell disease, cholesterol embolisation, genetic mutations, drugs (e.g., pamidronate, interferon), autoinflammatory conditions (e.g., systemic lupus erythematosus, haemophagocytic syndrome), and viral infections such as HIV, parvovirus B19, cytomegalovirus, Epstein–Barr virus, and, in recent times, SARS-CoV-2 (Table 1).[18]

Several case reports on COVAN have been published so far. Larsen et al.[19] reported a case of a 44-year-old female of an African American background who presented to the emergency department with fever, cough, vomiting, and flank pain. An acute kidney injury with haematuria and proteinuria was found, and an infection with SARS-CoV-2 was confirmed. Immunologic tests were negative. Due to worsening kidney function, renal replacement therapy with dialysis was started, and later on, a kidney biopsy was performed. Histological analysis showed a collapsing variant of FSGS with epithelial cell hypertrophy and signs of proximal tubular cell injury. No definitive viral inclusion particles were identified by electron microscopy. *APOL1* genotyping on the biopsy material was performed and the patient was found to be homozygous for the G1 risk allele. In the follow-up period, the patient's clinical status markedly improved, although they remained dialysis-dependent.[19]

In a report by Peleg et al.,[13] a case of a 46-year old male from a West-African background with severe kidney injury was presented. The patient complained of sore throat, malaise, fever, and vomiting 3 weeks before admission. Laboratory tests were notable for severe acute kidney injury with nephrotic-range proteinuria, hypoalbuminaemia, elevated lactate dehydrogenase, and elevated inflammatory markers. Hepatitis, HIV markers, and immunology were all negative. The patient was started on haemodialysis and, later on, a kidney biopsy was carried out. The biopsy findings were consistent with collapsing glomerulopathy with signs of mild to moderate tubulointerstitial oedema and arteriolosclerosis. Genotyping for the presence of *APOL1* high-risk alleles (G1 and G2) revealed that the patient was homozygous for the G1 allele. Due to respiratory symptoms and elevated inflammatory markers, a nasal swab for SARS-CoV-2 was performed, and it was positive. Later on, *in-situ* hybridisation for SARS-CoV-2

Table 1: Different forms of collapsing variant of focal segmental glomerulosclerosis.

Primary form
No identified cause
Seconary forms
Malignancies
Thrombotic microangiopathies
Sickle cell disease
Genetic causes
Cholesterol embolisation
Autoimmune causes (lupus, haemophagocytic syndrome)
Viral causes (SARS-CoV-2, HIV, parvovirus B19, CMV, EBV)

CMV: cytomegalovirus; EBV: Epstein–Barr virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

was performed on kidney tissue, which came back negative. No viral inclusion particles were detected by electron microscopy.[13]

Kissling et al.[20] presented a case of a 63-year-old Black male who was admitted due to SARS-CoV-2 pneumonia. In the first few days of hospitalisation, they developed a rapidly progressive acute kidney injury with nephrotic-range proteinuria (5 g/L). The patient's kidney biopsy showed collapsing glomerulopathy with acute tubular necrosis. In this case, electron microscopy showed several viral inclusion particles in the podocytes, consistent with SARS-CoV-2. Further work-up showed that the patient was homozygous for the *APOL1* G1 high-risk allele. The patient's kidney function improved later on and they did not need renal replacement therapy.[20]

Magoon et al.[21] presented two cases of collapsing FSGS in patients with COVID-19. A 28-year-old female of an African American background presented to the emergency department with fever, fatigue, shortness of breath, and cough. The patient had normal creatinine and nephrotic proteinuria at admission. Due to the clinical picture and bilateral opacities on the chest X-ray, a nasal swab for SARS-CoV-2 was performed and it came back positive. In the next 4 days, their creatinine level started to rise, and they were put on haemodialysis on Day 7. A kidney biopsy was performed to determine the cause of proteinuric acute kidney injury. A collapsing variant of FSGS was found and no viral inclusion particles were detected with electron microscopy. All of the other work-up, hepatitis and HIV markers, and immunology came back negative. The patient was later found to be homozygous for the *APOL1* G1 high-risk allele. They remained dialysis-dependent as their kidney function did not recover.

In the second case, a 56-year old African American male with SARS-CoV-2 infection and acute worsening of CKD and proteinuria was presented. Similar to the previous case, their kidney biopsy showed severe collapsing glomerulopathy with podocyte hypertrophy, and the electron microscopy did not show viral inclusion particles in this case either. The patient was found to be heterozygous for *APOL1* G1 and G2 alleles. Their kidney function did, however, improve, and they did not need dialysis after they were discharged from the hospital.[21]

Kudose et al.[22] performed a study on longitudinal outcomes of patients with COVAN and other associated podocytopathies. Out of the 23 patients with COVAN that were included, 21 of them (91%) were Black and two (9%) were White. Most of the patients had the high-risk *APOL1*

Table 2: Crucial characteristics of COVID-19-associated collapsing glomerulopathy.

Moderate or severe proteinuria (nephrotic-range)
Acute kidney injury or acute worsening of previous chronic kidney disease
Arterial hypertension
Oedema
High-risk *APOL1* genotype

genotype. According to their findings, 50% of the patients remained dialysis-dependent after hospital discharge.[22]

The most important characteristics of COVID-19-associated collapsing glomerulopathy were gathered by the authors of this paper (Table 2). Judging by the case reports presented thus far, the *APOL1* high-risk genotype is of crucial significance in the development of COVAN. Due to the greater prevalence of high-risk *APOL1* alleles in patients with an African American heritage, COVAN is more common in these patients, with a few cases described in White patients as well.[22] The authors found no data suggesting the presence of COVAN in other ethnicities and/or races. In an experimental model of a 'two-hit' hypothesis, the *APOL1* risk variant acts as a 'first hit' and the infection with a virus (such as SARS-CoV-2) acts as a 'second hit' through cytokine and chemokine release, ultimately resulting in podocyte dedifferentiation, proliferation, and hypertrophy.[18,23]

In majority of the cases, viral inclusion bodies were not detected on renal histology. Immune system dysregulation with consequent cytokine release, and not the viral presence per se, is most likely the trigger that leads to impairment in glomerular cell autophagy, mitochondrial function, and cell injury.[4,24] It appears that even anti-SARS-CoV-2 vaccines can lead to immune system activation and collapsing glomerulopathy in at-risk patients.[25]

Patients with homozygosity for *APOL1* risk alleles would likely benefit from prompt anti-viral and/or anti-inflammatory treatment to prevent the cytokine storm and the development of kidney impairment. Further studies are needed to determine the role of *APOL1* genotyping in certain patient groups in order to employ an optimal treatment strategy.[24]

CONCLUSION

COVAN is a new and emerging clinical entity, related to the SARS-CoV-2 infection. It can present as acute kidney injury or acute worsening of pre-existing CKD with marked proteinuria, usually in the nephrotic range. The COVAN pathophysiological features are associated with *APOL1* high-risk genotype, often found in patients with African heritage. Kidney biopsy shows collapsing glomerulopathy with podocyte proliferation, with or without SARS-CoV-2 viral inclusion particles. Treatment is supportive. Further studies are needed to improve the recognition of these patients and to develop optimal treatment strategies.

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Low-Dose Dopamine in the Management of Intradialysis Hypotension: A Retrospective Cohort Study in Nigeria

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Abstract

Introduction: Intradialytic hypotension (IDH) still remains a common finding in maintenance haemodialysis despite improvements in dialysis delivery. Measures are needed to minimise some aftermath of IDH like dialysis termination, which can impact poorly on dialysis outcome.

Methods: This retrospective study assessed IDH in a low-income setting, and compared two cohorts of IDH with and without dopamine treatment.

Results: Of the 416 participants, 92 (22.1%) had at least an episode of symptomatic IDH. Of these, 20 (21.7%) were treated with dopamine. Of the 2,205 sessions, 468 (21.2%) had symptomatic IDH, of which 63 (13.4%) with severe IDH were treated with dopamine. The mean age of all participants and dopamine treatment participants were 50.8 ± 9.3 years and 64.6 ± 9.5 years, respectively (P=0.001). Blood pressure (BP) reductions following dialysis were more with females (P=0.04). Dialysis dose was adequate in 7.9% and 4.2% of sessions with and without dopamine (P<0.001). Improvements in glomerular filtration rate were greater in dopamine-treated sessions (P=0.03 and P=0.04, respectively). Fewer anti-hypertensives (aOR: 14.64; 95% confidence interval [CI]: 7.88–20.41), low predialysis systolic (aOR:5.59; 95% CI: 3.88–9.41), and diastolic blood pressure (aOR: 5.78; 95% CI: 4.06-9.81) were independently associated with dopamine-treated sessions.

Conclusion: IDH was found in 21.2% of dialysis sessions. 13.4% with severe IDH had dopamine treatment. Participants with dopamine-treated sessions had fewer dialysis terminations and hospitalisations, and dopamine treatment improved the prescribed

dialysis and gave higher dialysis doses. Considering the economic effects of dialysis termination in low-income nations, intradialytic dopamine could be very beneficial.

Key Points

1. The prevalence of intradialytic hypotension (IDH) in Nigeria is reported to be 31.3% and 19.4% using The National Kidney Foundation's Kidney Disease Outcome Quality Initiative guidelines.

2. IDH is more prevalent in the presence of comorbidities, particularly cardiovascular disease.

3. Individuals with dopamine-treated sessions are more likely to have fewer dialysis complications, and a higher blood flow rate, ultrafiltration volume, and dialysis dose.

INTRODUCTION

Intradialysis hypotension (IDH) commonly complicates haemodialysis treatment, and could be associated with dysfunction of the central nervous, cardiovascular, and gastrointestinal systems; worsening of renal function; loss of vascular access; inadequate dialysis, poor quality of life; and death.[1] The National Kidney Foundation's (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) guidelines in 2005 defined IDH as an intradialytic fall in systolic blood pressure (BP) ≥20 mmHg or of mean arterial pressure ≥10 mmHg, leading to emergence of symptoms.[2]

The prevalence of IDH is estimated to range from 8%–40% based on a wide range of diagnostic criteria involving BP values only, or with symptoms, or further still with nursing intervention.[3-5] In the authors' local environment, the prevalence of IDH is reported to be 31.3% and 19.4% using the NKF-KDOQI criteria, and 8.6% using the European Best Practices Guidelines (EBPG).[6-8] The absence of a consensus definition has limited the scope of research on IDH and its outcome. However, Flythe et al.[10] reported that the nadir BP was more predictive of future mortality of the eight IDH definitions they reviewed.

With ultrafiltration, inadequate compensation by the heart, blood vessels, and splanchnic bed that mediate plasma refilling and/or augmentation of the venous return leads to IDH.[11] The compensatory activation of the sympathetic nervous system and the renin angiotensin aldosterone systems mediates vasoconstriction, leading to increased resistance in the peripheral, renal, and splanchnic circulations, and resulting in increased venous return, preload, and the cardiac output.[12, 13]

Despite advances in dialysis delivery, IDH is reported to be frequent in about 8% of the dialysis population.[14] IDH is more prevalent in the presence of comorbidities, particularly cardiovascular disease, hence KDOQI recommended that patients on maintenance haemodialysis should have a cardiovascular assessment with an echocardiogram every 3 years.[15] Heart failure is reported to increase the risk of frequent hospitalisation and poor outcome in treatment with inotropes like dopamine, just as dopamine is reported to be ineffective, or even harmful, when used to treat cardiac failure or acute kidney injury.[16-18] Pharmacological-based strategies used in managing IDH in the past included enhancing left ventricular relaxation in patients with left ventricular hypertrophy (LVH) using verapamil, reducing the heart rate using atenolol, decreasing the predialysis systolic BP using amlodipine, and stimulating α-1 adrenergic receptor agonist using droxidopa.[19-22] Other measures taken in the past included using carvedilol in the BLOCADE pilot study,[23] and increasing the numbers of BP-lowering drugs in patients with poorly controlled BP, in a Japanese study.[24] Despite other benefits that were seen in these studies, they were all reported to be non-effective in improving IDH.

Adenosine A1 receptor antagonist, FK352, was associated with improved rates of IDH, similar to anti-diuretic hormone (ADH) that allowed higher ultrafiltration rates.[25,26] The increased serum osmolality associated with thirst and increased interdialytic weight gain limited its continued use.[27]. Midodrine, an α-1 adrenergic receptor agonist prodrug, given predialysis, improved IDH and increased nadir systolic BP, but had no effect on the dialysis dose.[28] Its usefulness prompted the American Society of Nephrology (ASN) to contest midodrine's withdrawal by the U.S. Food and Drug Administration (FDA).[29,30] Dobutamine had also be reportedly used in managing frequent IDH, with some successes.[31]

Dopamine, a naturally occurring adrenergic agent, is used in medical, surgical, and most commonly in intensive care units to manage hypotension and shock.[32,33] In Nigeria, as in many low-income nations (LIN), about 90% of the dialysis population is not on any health insurance scheme.[34-36] A commonly feared side effect of dopamine is tachycardia, seen mostly in its medium and high doses, and around which many of its other adverse effects like arrhythmias and cardiac toxicity are hinged.[37] Dopamine use in treating IDH is scarcely reported. The authors hypothesise that low-dose dopamine regimen is effective and safe in managing IDH. This study compared sessions with IDH with and without dopamine treatment.

MATERIALS AND METHODS

This was a 3-year retrospective cohort study in which the dialysis sessions of patients between 16–78 years old, with CKD diagnosed according to the KDOQI 2012 criteria,[33] who received maintenance haemodialysis between August 2018–July 2021 at the dialysis suite of Babcock University Teaching Hospital, Ilishan-Remo, Nigeria, were studied. The sessions were grouped into three cohorts as no IDH, IDH without dopamine (IDHWD), and dopamine-treated sessions (DTS).

Participants' case notes and dialysis chats were retrieved, and variables obtained were age, gender, cause and type of kidney disease, percent oxygen saturation (SPO_2) pulse rate (PR) BP predialysis and, every quarter of an hour throughout dialysis. Also retrieved were the number of hospitalisation, comorbidities, total dose of dopamine per dialysis, and duration of dopamine use per dialysis. The results of pre- and postdialysis renal biochemistry, electrocardiogram (ECG), and echocardiogram were also retrieved.

Excluded were sessions with predialysis dopamine infusion, intradialysis hypertension, or sessions with other inotropes.

Inclusion criteria for dopamine treatment was ≥three consecutive episodes of severe IDH (intradialysis drop in SBP ≥20 mmHg to <100 mmHg with symptoms, and in which nursing interventions were unsuccessful leading to dialysis termination, after ruling out and/or correcting modifiable factors such as fever, drug effect, or food intake).[34-36] Dopamine 2-5 ug/kg/min in 200 ml of 0.9% saline was commenced whenever the SBP fell by ≥20 mmHg or SBP <90 mmHg, with symptoms such as nausea, yawning, cramps, dizzy spells, syncope, body pains, and/or chest discomfort that did not respond to routine treatment measures. Intradialysis anticoagulation was with unfractionated heparin (5,000 IU). The dialysate flow rate (DFR) was 500 ml/min for all sections, and the dialysate sodium, potassium calcium, and bicarbonate were 140 mmol/L, 2.0 mmol/L, 2.0 mmol/L, and 34 mmol/L, respectively. Whenever sodium profiling was carried out, the mean dialysate sodium concentration was documented.

The study was approved by the Babcock University Human Research Ethics committee (BUHREC/723/19, NHREC/24/01/2018).

DEFINITIONS

Tachycardia: Mild (PR: 101–119/min)
Moderate (PR: 120–139/min)
Severe (PR: 140–149/min)
Life-threatening (PR ≥150/min)[37]

Hypoxaemia: SPO_2 <95%[38]

Dopamine: Low dose: <5 ug/kg/min
Medium dose: 5–9 ug/kg/min
High dose: ≥10 ug/kg/min[39]

Targeted weight loss: Predialysis weight plus volume of administered fluid minus UFV[40]

IDH: ≥20 mmHg intradialysis fall in SBP[1]

Severe IDH: ≥3 consecutive episodes of intradialytic drop in SBP ≥20 mmHg to <100 mmHg with symptoms, in which nursing interventions were unsuccessful leading to dialysis termination (after ruling out and/or correcting modifiable factors such as fever, drug effect, or food intake), requiring the need for inotropic support[36]

Anaemia: hematocrit <33%[41]
Hypoalbuminaemia: <35 mg/dl[42]

Dialysis dose: Normal (Kt/V ≥1.2), low (Kt/V 0.9–1.1), and very low (Kt/V <0.9)[43]

Hypertension-associated CKD: Longstanding hypertension that led to kidney disease common in elderly and late middle-aged patients

Chronic glomerulonephritis: Kidney disease complicated by hypertension, common in the young and in early middle age, with or without antecedent history of pharyngitis or skin sepsis

In this study, hospitalisation is defined as hospital admission lasting up to 24 hours. All 557 participants had an ECG, but only 43 (7.72%) had an echocardiogram, on account of cost.

STATISTICAL ANALYSIS

Data was analysed using SPSS version 22.0 (IBM, California, USA). Continuous variables with means and standard deviations were compared using T-test. Categorical variables as proportions and percentages were compared using Chi-square test or Fisher's exact test when variables were less than five. The P value <0.05 was considered statistically significant. Variables with P <0.025 were entered into a multiple regression model to determine predictors of dopamine use in IDH, using backward elimination to adjust for confounders.

RESULTS

Two thousand two hundred and five sessions by 416 participants were studied. Ninety-two (22.1%) participants had ≥1 episode of symptomatic IDH. Of the participants with symptomatic IDH, 20 (21.7%) were treated at least once with dopamine. Of the 2205 sessions, 1737 (78.8%) had no IDH, 468 (21.2%) had symptomatic IDH, and of this, 63 (13.4%) with severe IDH had dopamine treatment (Table 1). The mean age of all participants, participants with no IDH, participants with IDHWD, and with DTS were 50.8 ± 9.3 years, 49.6 ± 7.5 years, 53.8 ± 8.7 years, and 64.6 ± 9.5 years, respectively (P=0.001). The mean age of the 11 (55.0%) males and 9 (45.0%) females with DTS were 63.8 ± 7.7 years, and 65.5 ± 8.3 years (P=0.04).

Predialysis, DTS had more hypoxaemia compared to sessions with IDHWD (P=0.05). Postdialysis, sessions with IDHWD had more hypoxaemia than DTS (P=0.001). The mean predialysis systolic BP of males and females with DTS were 119.3 ± 7.5 mmHg versus 118.3 ± 5.9 mmHg (P=0.13); postdialysis, these were 120.0 ± 22.9 mmHg and 117.5 ± 22.8 mmHg (P=0.04). The mean predialysis diastolic BP of males and females in DTS were 75.3 ± 4.6 mmHg and 73.3 ± 4.0 mmHg (P=0.05); postdialysis, these were 75.3 ± 5.9 mmHg and 69.5 ± 22.8, P=0.001. The dialysis dose was adequate in 335 (15.2%), 313 (18.0%), 17 (4.2%), and five (7.9%) of all sessions, sessions without IDH, sessions with IDHWD, and DTS, respectively (P<0.001). Three hundred and twenty nine (79.1%) participants had LVH using the Sokolow–Lyon criteria on the ECG. Of the 43 participants that had echocardiogram, eight (18.6%) had ejection fraction <50%, 33 (76.7%) had concentric LVH, four (9.3%) had diastolic dysfunction, one (2.3%) had systolic dysfunction, and 27 (81.8%) had combined systolic and diastolic dysfunction. The 18 (4.3%) participants with echocardiogram confirmed heart failure had 8.1% of the sessions with IDH but without dopamine, while 14.3% had IDH with dopamine treatment. The 39 (9.4%) participants with diabetes had 20.0% of the sessions with IDH but without dopamine, while 36.5% had IDH with dopamine treatment.

Following dialysis, the rise in mean serum sodium and fall in mean urea were more with DTS than sessions with IDHWD (P=0.07 and

Table 1: Sociodemographic, historical, and clinical characteristics of study population.

Variable	All participants	All sessions	No IDH	IDHWD	DTS	p value
	N=416 (%)	N=2,205 (%)	N=1,737 (%)	N=405 (%)	N=63 (%)	
Sex						
Males	272 (65.4)	1,466 (66.4)	1,194 (68.7)	238 (58.5)	34 (54.0)	0.002
Females	144 (34.6)	739 (33.6)	543 (31.3)	167 (41.5)	29 (46.0)	
Age (years)						
16–39	98 (23.6)	468 (21.2)	410 (23.6)	52 (12.8)	6 (9.5)	0.001
40–64	238 (57.2)	1,311 (59.5)	1,039 (59.8)	241 (59.5)	31 (49.2)	
>65	80 (19.2)	426 (19.3)	288 (16.6)	112 (27.7)	26 (41.3)	
Aetiology						
HTN	183 (44.0)	976 (44.3)	822 (47.3)	136 (33.6)	18 (28.6)	0.001
CGN	147 (35.3)	740 (33.5)	612 (35.2)	119 (29.4)	9 (14.3)	
DM	39 (9.4)	218 (9.9)	114 (6.6)	81 (20.0)	23 (36.5)	
Others	47 (11.3)	271 (12.3)	189 (10.9)	69 (17.0)	13 (20.6)	
HD/week						
<3	345 (82.9)	1,742 (79.0)	1,330 (76.6)	356 (87.9)	56 (88.9)	0.03
3	71 (7.1)	463 (21.0)	407 (23.4)	49 (12.1)	7 (11.1)	
EPO/week						
<3	364 (87.5)	1,784 (80.9)	1,363 (78.5)	364 (89.9)	57 (90.5)	0.01
3	52 (12.5)	421 (19.1)	374 (21.5)	41 (10.1)	6 (9.5)	
Anti-hypertensives						
1	31 (7.4)	172 (7.8)	77 (4.4)	54 (13.3)	41 (65.1)	0.001
2	158 (38.0)	753 (34.1)	563 (32.4)	172 (42.5)	18 (28.6)	
≥3	227 (54.6)	1,280 (58.1)	1,097 (63.2)	179 (44.2)	4 (6.3)	
Pre-dialysis SPO_2 (%)	N/A	N/A	N/A	N/A	N/A	N/A
<95		1,958 (88.8)	1,526 (87.9)	373 (92.1)	59 (93.7)	0.05
≥95		247 (11.2)	211 (12.1)	32 (7.9)	4 (6.3)	
Post-dialysis, SPO_2 (%)	N/A					
<95		1,402 (63.6)	1,074 (61.8)	287 (70.9)	41 (65.1)	0.001
≥95		803 (36.4)	663 (38.2)	118 (29.1)	22 (34.9)	
Pre-dialysis PR		86.6±9.5	85.9±9.0	87.8±7.4	98.1±8.4	0.03
Post-dialysis PR		89.4±7.4	89.1±7.0	90.0±9.4	98.1±10.3	0.04
Pre-dialysis systolic BP (mmHg)						
<140		416 (18.9)	219 (12.6)	160 (39.5)	48 (76.2)	<0.001
≥140		1,789 (81.1)	1,518 (87.4)	245 (60.5)	15 (23.8)	
Pre-dialysis diastolic BP (mmHg)						
<90		294 (13.3)	149 (8.6)	107 (26.4)	38 (60.3)	<0.001
≥90		1,911 (86.7)	1,588 (91.4)	298 (73.6)	25 (39.7)	
Systolic BP (mmHg)						

Table 1 continued

Variable	All participants	All sessions	No IDH	IDHWD	DTS	p value
Pre-dialysis		143.5±17.8	149.3±17.5	126.3±9.5	98.18±10.3	<0.001
1 hour ID		134.6±9.7	140.6±11.4	116.2±7.7	101.7±11.8	0.002
2 hour ID		129.6±6.3	135.7±7.5	108.8±7.2	108.2±6.7	0.004
3 hour ID		125.2±7.4	130.0±9.3	105.6±7.8	116.5±4.9	0.003
Post-dialysis		125.6±6.1	131.2±4.3	102.9±5.2	118.6±6.5	0.002
Diastolic BP (mmHg)						
Pre-dialysis		95.8±6.3	98.0±10	89.7±6.8	74.4±6.6	<0.001
1 hour ID		91.1±6.2	94.2±7.0	81.4±7.1	67.8±5.5	<0.001
2 hour ID		83.3±3.9	85.8±9.9	74.8±6.5	71.2±3.5	0.002
3 hour ID		84.7±7.7	88.0±7.5	72.4±6.3	72.2±3.8	0.004
Post-dialysis		84.6±9.2	88.3±5.4	70.8±6.4	71.8±5.4	0.003

BP: blood pressure; CGN: chronic glomerulonephritis, DM: diabetes; DTS: dopamine-treated sessions; EPO: erythropoietin; HD: haemodialysis; HTN: hypertension; ID: intradialysis; IDH: intradialysis hypertension; IDH-WD: intradialytic hypotension without dopamine; PR: pulse rate; SPO_2: percent oxygen saturation.

P=0.05, respectively). The rise in mean SBC and fall in mean potassium were more in sessions with IDHWD than DTS (P=0.09 and P=0.1, respectively). There was a greater fall in mean anion gap in DTS compared to sessions with IDHWD (P=0.04). The fall in mean serum creatinine and the rise in mean GFR was more with DTS than IDHWD (P=0.04 and P=0.03, respectively). There was a greater increase in the hematocrit in DTS than sessions with IDHWD (P=0.05). The mean yearly hospitalisation per participant for all, those without IDH, participants with IDH without dopamine, and those with dopamine were 2.73 ± 1.23, 2.67.11 ± 1.21, 2.94 ± 1.24, and 2.88 ± 1.22, respectively (Table 2 and Table 3).

In the multiple regression analysis, fewer antihypertensives (aOR: 14.64; 95% CI: 7.88–20.41; P<0.001) low predialysis systolic BP (aOR: 5.59; 95% CI: 3.88–9.41; P-0.001), and low predialysis diastolic BP (aOR: 5.78; 95% CI: 4.06–9.81; P-0.001) were independently associated with DTS.

DISCUSSION

The incidence of symptomatic IDH was 21.2%; of this, 13.5% of patients with severe IDH were managed with dopamine. The mean blood flow rate, ultrafiltration volume, dialysis duration, and the dialysis dose were higher in DTS, while the frequency of dialysis termination was less with the DTS compared to sessions with IDHWD. The risk of intradialytic death was marginally higher in the DTS. Females, the elderly, and diabetics were more likely to develop IDH, and to require dopamine treatment. Participants with predialysis hypoxaemia were more likely to develop IDH and require dopamine. Under-dialysis, lesser erythropoietin use, fewer antihypertensives, and lower predialysis BP were associated with IDH and dopamine use.

The frequency of symptomatic IDH falls within the very wide range reported in previous studies, but higher than the 10.1% reported by Kuipers et al.[44] for the EBPG, and lower than the 31.3% found in a study in Nigeria.[6] The lower rate in the EBPG compared to this study is expected, considering the association of several limiting factors in LINs

Table 2: Dialysis prescription, intradialytic events, and outcomes in patients.

Variable	All sessions	No IDH	IDHWD	DTS	p value
	N=2,205 (%)	N=1,737 (%)	N=405 (%)	N=63 (%)	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Duration (hour)	3.9±1.1	3.9±1.0	3.7±1.3	3.8±1.0	0.04
BFR (mL/min)	351.6±12.6	358.3±14.4	324.7±10.9	344.2±9.5	0.001
UFV (L)	2.8±1.4	2.9±1.8	2.2±1.0	2.6±1.4	<0.001
Access type					
AV fistula	204 (9.3)	137 (7.9)	50 (12.3)	7 (11.1)	0.001
TIJVC	807 (36.6)	612 (35.2)	178 (44.0)	27 (42.9)	
Non-TIJVC	128 (5.8)	85 (4.9)	39 (9.6)	4 (6.3)	
Femoral catheter	1066 (48.3)	903 (52.0)	138 (34.1)	25 (39.7)	
ID death	6 (0.3)	0 (0.0)	5 (1.2)	1 (1.6)	0.04
HD termination	40 (1.8)	23 (1.3)	15 (3.7)	2 (3.2)	<0.001
Hospitalisations/year	1144 (2.8)	874 (2.70)	212 (2.94)	58 (2.90)	0.08
Dialysis dose (Kt/V)	1.12 ± 0.47	1.17 ± 0.51	0.91 ± 0.44	1.10 ± 0.44	0.001

AV: arterovenous; BFR: blood flow rate; DTS: dopamine-treated sessions; HD: haemodialysis; ID: intradialytic; IDH: intradialytic hypotension; IDHWD: intradialytic hypotension without dopamine; TIJVC: tunneled internal jugular vein catheter; UFV: ultrafiltration volume.

that would normally entail higher rates of dialysis complications like IDH. One would have expected a higher rate compared to findings by Okpa and his group,[6] since intradialysis hypertension was excluded in this study, but the subjective nature of symptom reportage and perhaps the acceptance of these by the dialysis team could differ widely between centres.[10]

The 13.4% prevalence of severe IDH in this study falls within the 8% and the 17.2% classified as frequent IDH by Kuipers et al.,[44] and Sands et al.[45] The 20 participants with DTS met the 20% of dialysis sessions cut-off criteria of the EBPG, for diagnosis of frequent IDH. The non-responsiveness of their dialysis sessions to routine IDH treatment regimen, except with inotropic support, is in agreement with Allapan et al.,[46] who managed severe IDH with midodrine.

The mean dialysis duration of the DTS was higher than the sessions with IDHW, and this reflected the lower risk of dialysis termination in the DTS. This agrees with findings by Anandh et al.,[31] who reported that dobutamine was effective in reducing the episodes of severe IDH (SBP <90 mmHg), admission rates, and left ventricular ejection fraction. The higher BFR in the DTS compared with the IDHWD in this study agrees with Cruz et al.,[47] who reported that with midodrine (an inotrope), higher BFR could be achieved, as the increased risk IDH from a rising BFR is prevented with an inotropic support that increases the heart rate, peripheral resistance, and the cardiac output through increased sympathetic activities. The higher UFV in the DTS than the IDHWD reflects the ability of inotropes to prevent the BP reduction that would have been enough to meet the BP diagnostic criteria of IDH.[32, 33]

The higher dialysis dose in the DTS is not in

agreement with previous findings.[23] Renal dose dopamine mediates vasodilatation and increased intradialysis renal blood flow, augments residual renal function contributes to solute and water clearance and dialysis dose.[34,35] This is less significant with dobutamine which mediates more of chronotropic activities leading to higher cardiac output, thereby reducing the risk of IDH, but with lesser effect on renal blood flow and residual renal function.[31]

The combination of longer dialysis duration, and higher BFR and UFV in the DTS compared with IDHWD, explains the higher dialysis dose. The smaller BP difference in the DTS following dialysis confers a lesser risk of ischaemic organ dysfunction. It could reduce the incidence of dialyser blood clotting and vascular thrombosis.[48-50]

Though all deaths in sessions with IDH (with and without dopamine) were associated with intradialytic hypotension, it is worth noting that the only death in DTS was that of a 62-year-old female with disseminated ovarian cancer.[51] Choi et al.,[52] in a review of several findings from studies involving dopamine use associated with kidney function, suggested a nephroprotective effect of dopamine. Low-dose dopamine acting on the D-1 and D-2 like receptors induces sodium and water excretion, increases renal perfusion and stabilises BP, all of which are treatment targets in kidney disease.

The inverse relationship between the frequency of dialysis and IDH could be attributable to the shorter interdialytic periods, lesser interdialytic weight gain, lower osmotic gradients, lesser UFV, and therefore lower risk of IDH.[53] The inverse relationship between the number of BP lowering drugs and the risk of IDH (and dopamine use), tend to suggest either a cardiac decompensation or autonomic dysfunction particularly baroreceptors mediated, as strictly renal diseases, though rare, commonly present with poor BP control, particularly in end stage disease, and more so in the Black population.[54] However, this relationship depicts more of an 'effect' rather than a 'causal' one, as the increased risk and/or the occurrence of IDH necessitated the reductions in the number of anti-hypertensives.

Fewer erythropoietin use, commonly associated with severe anaemia, is complicated by higher plasma volume that would necessitate higher UFV.[55] Similarly, higher viscosity from frequent erythropoietin use would be more likely to induce sluggish flow, dialyser blood clotting, and elevated blood pressure, and at times dialysis termination.[56] Agarwal et al.[57] in their findings noted an positive relationship between the hematocrit and the risk of IDH.

Dialysis termination is not uncommon, and could be a very distressing occurrence in LINs when one considers the difficulty some of the patients pass through to secure funds for a dialysis session.[6-8] The practice of fresh payment for every new dialyser, that is common in almost all dialysis centres in this clime, makes all attempts at preventing dialysis termination a worthwhile task.[6] The greater risk of IDH and dopamine treatment in diabetes and heart failure in this study agrees with previous findings, and could be associated with neuropathy-induced neurovascular abnormalities and cardiac remodelling, leading to diastolic and systolic dysfunction associated with lower cardiac output and ejection fraction.[58,59] However, the relative absence of tachycardia would have limited any unwanted effects associated with these diseases.[33]

The better treatment outcome of participants that were treated with low-dose dopamine in this study was mostly secondary to increased BP that allowed for higher BFR, UFV, and longer dialysis time. This all led to higher dialysis dose, and lower dialysis termination and hospitalisation rates, on a background of mild or no tachycardia, as were reported in previous studies.[29,30]

Several limitations were encountered in this study. The retrospective design, the absence of newer devices for monitoring/treating IDH like hematocrit monitoring, bioimpedance, and biofeedback ultrafiltration were unavailable. Participants' dry weight and residual kidney function were not assessed during dialysis sessions. The dialysis suite had no dialysate cooling machine. Cardiac enzymes (troponins and creatinine kinase-MB) were not assayed. The blood PH, the best measure to assessed metabolic acidosis, was not assessed. The inclusion of IDH prone participants added to the strength of this study.

Table 3: Relationship between dialysis dose and correlates of intradialysis hypotension.

Variables	IDHWD	DTS	OR	95% CI	p value
	N=405 (%)	N=63 (%)			
Sex					
Males	238 (87.5)	34 (12.5)	0.04	0.03-0.10	0.09
Females	167 (85.2)	29 (14.8)			
Age (years)					
<65	293 (88.8)	37 (11.2)	2.96	1.89–4.24	0.04
≥65	112 (81.2)	26 (18.8)			
Diabetes					
Yes	81 (77.9)	23 (22.1)	4.36	1.044–5.83	0.002
No	324 (89.0)	40 (11.0)			
Antihypertensives					
1	54 (56.8)	41 (43.2)	10.3	4.43–13.97	<0.001
≥2	351 (94.1)	22 (5.9)			
Haemodialysis/week					
<3	356 (86.4)	56 (13.6)	0.01	0.007–0.029	0.9
≥3	49 (87.5)	7 (12.5)			
Erythropoietin/week					
<3	364 (86.5)	57 (13.5)	0.01	0.01	1.0
≥3	41 (87.2)	6 (12.8)			
Oxygen saturation (%)					
<95	373 (86.3)	59 (13.7)	0.05	0.015–0.09	0.07
≥95	32 (88.9)	4 (11.1)			
Pre-dialysis systolic BP (mmHg)					
<140	160 (76.9)	48 (23.1)	4.761	2.34–7.94	<0.001
≥140	245 (94.2)	15 (5.8)			
Pre-dialysis diastolic BP (mmHg)					
<90	107 (73.8)	38 (26.2)	4.864	1.18-6.86	<0.001
≥90	298 (92.3)	25 (7.7)			
Dialysis dose (Kt/V)					
<1.2	388 (87.0)	58 (13.0)	3.15	3.03–5.94	0.03
≥1.2	17 (77.3)	5 (22.7)			
Dialysis termination					

Table 3 continued

Variables	IDHWD	DTS	OR	95% CI	p value
Yes	15 (88.2)	2 (11.8)	0.2	0.01–0.98	0.07
No	390 (86.5)	61 (13.5)			
Hospitalisation					
Yes	212 (78.5)	58 (11.5)	3.04	2.91–5.14	0.04
No	193 (97.4)	5 (2.6)			
Intradialysis death					
Yes	2 (66.7)	1 (33.3)	5.8	2.63–8.22	<0.001
No	403 (86.7)	62 (13.3)			

BP: blood pressure; CI: confidence interval; DTS: dopamine-treated sessions; IDH: intradialysis hypotension; IDHWD: intradialytic hypotension without dopamine. OR: odds ratio.

CONCLUSION

Intradialytic hypotension is still common. The authors found a frequency of 21.2%, and of this 13.4% had severe IDH requiring inotropic support. Diabetes, heart failure, female gender, advancing age, low predialysis blood pressure, fewer dialysis, and erythropoietin treatment were associated with IDH and dopamine treatment. Participants with DTS were more likely to have fewer dialysis terminations and hospitalisations, and higher BFR, ultrafiltration volume, and dialysis dose. Considering the economic effect of dialysis termination on the dialysis population in LINs, the use of low-dose intradialytic dopamine infusion (which has the added advantage of increasing the dialysis dose) could be of benefit.

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Pathophysiology of Diabetic Kidney Disease

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Abstract

Diabetic kidney disease (DKD) has been an immense burden on the healthcare system, and is the leading cause of end stage kidney disease worldwide. DKD involves various intersecting pathways that lead to progressive kidney damage. Due to its versatile pathogenesis, DKD has been a formidable adversary. For many decades, there has not been much development in the arsenal in the fight against DKD, but recently, multiple new prospects have emerged due to the breakthrough in understanding of DKD pathology.

Tireless research of the changes occurring in the kidney as a result of diabetes, and the factors driving these changes, has led to the invention of medications that hopefully will be highly impactful in preventing end stage kidney disease in patients with diabetes. In this review, the authors summarise the timeline of the pathological changes that occur in DKD, the mechanism driving these pathological changes, and the recent discoveries in the pathways leading to DKD. These span over changes in metabolic pathways, inflammatory cascades, epigenetic alterations, and the description of their effects at cellular to structural levels in the kidney as a byproduct of uncontrolled hyperglycaemia. The authors also correlate these mechanisms with a few of the medications that are being utilised to slow down DKD, and some in the pipeline, with some references to the trials that support their use.

Key Points

1. Forty percent of patients with diabetes will have subsequent diabetic kidney disease (DKD). DKD involves various intersecting pathways that lead to progressive kidney damage, and is the leading cause of end-stage kidney disease worldwide.

2. High glucose levels impact haemodynamics, hormone production, metabolic pathways, oxidative stress, and inflammation. DKD damages the podocytes, glomeruli, and the tubules, as well as causing changes on the cellular level including mitochondrial injury and epigenetic changes.

3. Improving understanding of pathological pathways of DKD has informed development of targeted therapies.

INTRODUCTION

It is imperative to understand the pathway in order to alter the course. Diabetic kidney disease (DKD) has been a challenge for nephrology for the last three centuries, despite the discovery of diabetes much earlier, around 1500 BC.[1] A lot of progress has been made against the progression of DKD, but it still remains the most common cause of end stage kidney disease (ESKD) worldwide. In 2021, 9% of the healthcare budget in the USA was spent on diabetes, and the worldwide count rose to 537 million adult (20–79-year-old) patients.[2] Forty percent of patients with diabetes end up with DKD and 10% of patients with diabetes end up on dialysis. Of the ESKD population, 60–80% are either diabetic, hypertensive, or both.[2,3] In this review, the authors shed light on the recent advances in understanding the pathophysiology of DKD and summarise some of the correlating therapeutic interventions used across the globe.

TIMELINE OF DIABETIC KIDNEY DISEASE

Diabetes can go unnoticed and undiagnosed for years in the absence of appropriate screening. Similarly, it can take years before the effects of diabetes on the kidney can be picked up clinically, although the changes start soon after its onset. Even though DKD does not follow an exact timeline, patients with diabetes followed up for 10 years in the UK were noted to progress to microalbuminuria at a rate of 2% per year after the diagnosis of diabetes. Furthermore, the study noted that there was a 2.8% per year progression to macroalbuminuria from the microalbuminuria.[4] Fourteen percent of patients developed renal impairment without preceding microalbuminuria.[4] An autopsy study on 168 patients with diabetes noted that 63% of patients already had histological evidence of DKD, with almost 19% of those patients without any clinical evidence of DKD.[5] Patients with Type 2 diabetes are less predictable, mostly due to inaccuracy of diagnosis, while patients with Type 1 diabetes have been noted to follow a more predictable pattern of kidney injury. During the first 5–10 years, epidermal growth factor receptor (eGFR) can overestimate the kidney function due to hyperfiltration followed by a decrease in eGFR and hypertension, usually noticed around 15 years after diagnosis,[6] as described by the Mogensen classification of diabetic nephropathy. Increase in kidney size can start within 5 years of diagnosis with glomerular basement membrane expansion and mesangial thickening, taking about 10–15 years from onset. Overt fibrosis was noted after approximately 20 years of Type 1 diabetes.[6] Despite this general pattern, the course of DKD remains irregular. In many other studies, it was also noted that the decline in eGFR in more than 50% of patients with diabetes did not follow a linear pattern.

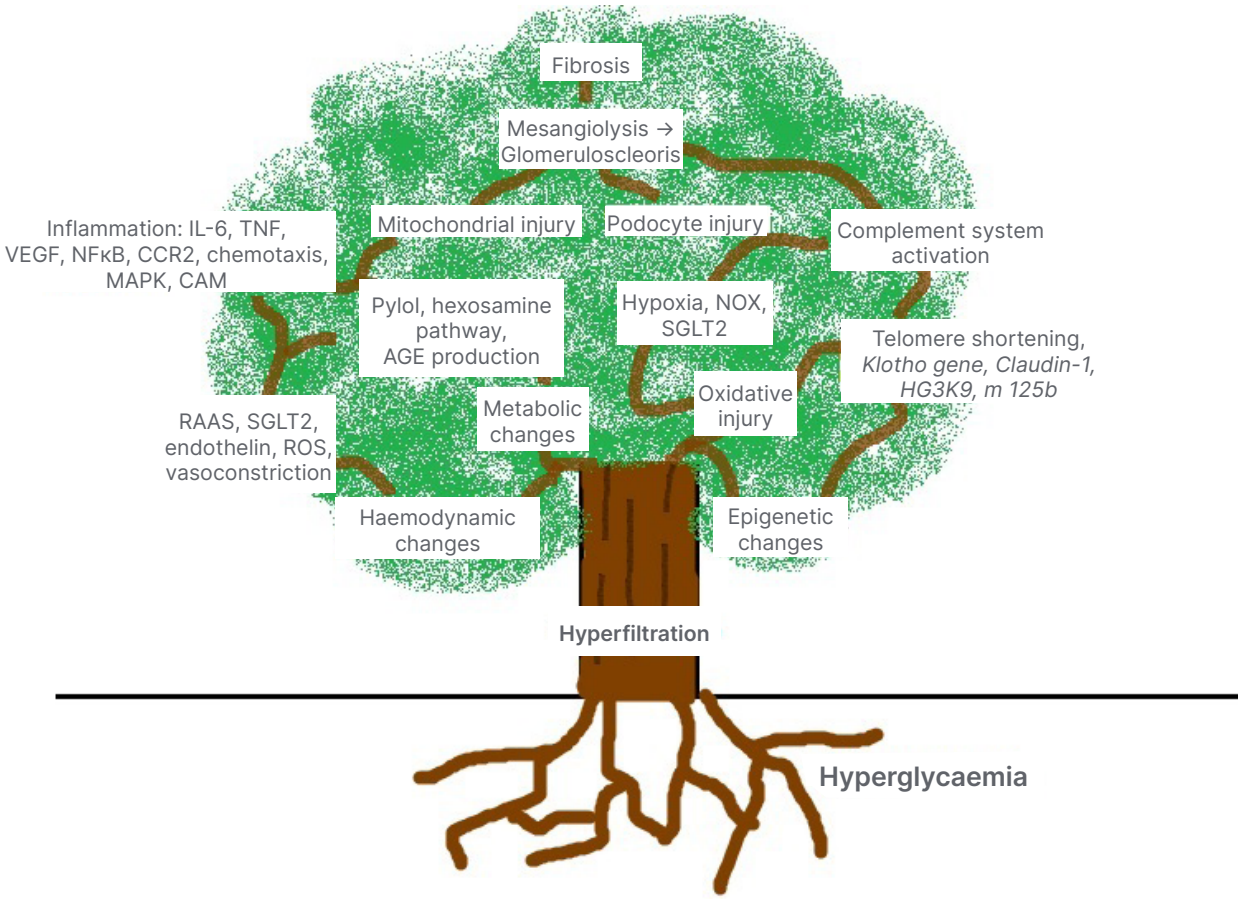
PATHOPHYSIOLOGY

Diabetes, a name coined from passing a lot of urine and mellitus (meaning sweet) speaks itself of uncontrolled blood glucose levels. The end result of uncontrolled hyperglycaemia in the kidney is nephron death. This manifests in the form of glomerulosclerosis, interstitial fibrosis, and tubular atrophy, but there are a lot of milestones and instigators along the way. Fibrosis is the end point of years of micro- and macroscopic changes resulting from the diabetic milieu, as noted in Figure 1. The inception of the renal involvement in this disorder is the onset of uncontrolled levels of blood glucose. The authors will discuss the framework that stems from hyperglycaemia, and concludes with renal fibrosis.

Hyperfiltration

Hyperglycaemia initiates its effects on the kidney by disturbing the osmotic forces. The higher blood glucose contents cause higher osmolality in the glomerular capillaries, resulting in higher glomerular pressures. This results in more outward forces increasing the glomerular filtration. Initially, this results in a falsely low to normal eGFR calculation based on more creatinine filtration with hyperglycaemia.[6] This hyperfiltration is proposed to be multifactorial. Chemokines and enzymes like ornithine decarboxylase, which are produced in response to hyperglycaemia (noted in the kidneys of mice with hyperglycaemia), bring about renal enlargement with increased filtration surface area per nephron.[7,8] Obesity, which can be integral to most patients with diabetes, can worsen renal enlargement and hyperglycaemia, promoting this initiation of renal injury.[4,9] Weight

Figure 1: Hyperglycaemia lays the roots in the pathogenesis of diabetic kidney disease.



Hyperglycaemia leads to hyperfiltration, which is followed by metabolic, hormonal, haemodynamic, inflammatory and epigenetic changes. Oxidative stress and hypoxia play a vital role. All these precipitate to podocyte injury, mitochondrial distress, tissue death, glomerulosclerosis, and interstitial fibrosis.

AGE: advanced glycation end products; CAM: cell adhesion molecules; CCR2: C-C chemokine receptor 2; MAPK: mitogen activated protein kinase; NFκB: nuclear factor κ B; NOX: nicotinamide adenine dinucleotide phosphate oxidases; RAAS: renin–angiotensin–aldosterone system; ROS: reactive oxygen species; SGLT2: sodium–glucose co-transporter 2; VEGF: vascular endothelial growth factor.

loss in patients with DKD, through surgical[9] or non-surgical methods in animal models, showed a significant reduction in the rate of decline in the eGFR.

Intraglomerular hypertension, which can be multifactorial, also predisposes to hyperfiltration. In many patients with diabetes, coexisting systemic hypertension,[4,9] increased intrabdominal pressure due to obesity,[10] and the increased osmotic pressures in the glomeruli end up contributing to this. Hyperglycaemia and protein-rich meals[11] result in the production of various chemicals that can impair tubule-glomerular feedback, and increase local vasoconstrictors.

Another mechanism for hyperfiltration is the role of sodium–glucose co-transporters 2 (SGLT2) found in the proximal convoluted tubules. With supraphysiological levels of blood glucose, there is an upregulation of SGLT2, resulting in the maximal utilisation of these transporters. Maximal reabsorption in the PCT causes decrease tubular pressures, causing more filtration from the glomerular vessel.[12] Also, with

maximal sodium and glucose reabsorption, there is decreased distal sodium delivery activating the renin–angiotensin–aldosterone system (RAAS).

This hyper-flow state also leads to protein leak, which instigates alteration in the nephron structure, with resultant mesangial hypertrophy seen in the kidneys of patients with diabetes.

Measures taken to control hyperglycaemia have been proven to inhibit DKD progression, myocardial infarction, and mortality.[13] Therefore, antihyperglycaemics have been the cornerstone in the management of DKD.

Haemodynamic Effects and Endothelial Injury

Hyperglycaemia and SGLT2-assisted decreased distal sodium delivery leads to activation of RAAS, producing efferent arteriolar vasoconstriction and afferent vasodilation, and amplifying intraglomerular hypertension. RAAS activation worsens systemic hypertension. Renin by itself has been noted to activate the mitogen activated protein kinase (MAPK) signalling pathway, while angiotensin II directly assists fibrosis by boosting transforming growth factor (TGF) production,[14] vascular endothelial growth factor (VEGF), cell adhesion molecules, nuclear factor κ B (NFκB) pathway, and toll-like receptors activation.[15] TGF-β keeps a check between fibrosis and inflammation, and any imbalance in the concentration of TGF-β leads to abnormalities amongst them. TGF-β acts via *SMAD3* and *SMAD7*. The former positively regulates non-coding RNA for inflammatory and fibrotic mediators, while the latter negatively affects it. Angiotensin II also stimulates production of reactive oxygen species (ROS) and inflammatory cellular attraction through activation of monocyte chemoattractant protein 1 (MCP-1), C-C chemokine receptor 2 (CCR2; in rat models),[16] and co-stimulation of NK and T cells (in human subjects).[17] In animal models and cultured kidney tissue, aldosterone was noted to facilitate fibroblast production by triggering TGF-β/*SMAD2*, fibronectin,[18] stimulating platelet derived growth factor receptor plus EGFR via phosphoinositide 3-kinases/MAPK signalling,[19] c-Jun N terminal kinase phosphorylation,[20] and epithelial-mesenchymal transition.[21] It also increases expression of plasminogen activator inhibitor-1, promoting hypercoagulable milieu.[22] Angiotensin and hyperglycaemia prompt endothelin production, worsening vasoconstriction, inflammation, podocyte injury, nephrin shedding, and interstitial fibrosis.[23]

Metabolic Changes

Diabetes is associated with dysregulation of multiple metabolic pathways. Hyperglycaemia brings about activation of pathways including RHO/ROCK, hexosamine, pylol, advanced glycation end products (AGE), and protein kinase C (PKC), producing higher ROS, generating higher levels of MAPK, JAK signal transducers and activators of transcription, and NFκB,[24] which are building blocks to inflammation and fibrosis. MAPK is linked to extracellular matrix production and podocyte injury.[25] NFκB signals production of adhesion molecules and cytokines like macrophage chemoattractant protein MCP-1, IL-6, and tissue necrosis factor α.[26] ROS also directly causes damage to cellular structures by oxidising various lipids, nucleic acids, and proteins. This lipid oxidation is aggravated with coexisting obesity and Type 2 diabetes, due to higher load of lipids.

Hypoxia and Oxidative Stress

Renal hypoxia is the inability of the oxygen supply to meet renal demands. This correlates directly with the blood supply, while the majority of demand depends on the metabolic activity in the tubules.

Hyperglycaemia can lead to oxidative stress and hypoxia in multiple ways. RAAS-mediated vasoconstriction causes ischaemic injury, hyperglycaemia causes hyperfiltration and tubular hypertrophy and overactivates SGLT2 channels, which depletes higher amounts of adenosine triphosphate and oxygen, leaving the nephron in a hypoxic state. An imbalance between antioxidants and ROS is a strong determinant for expediting tissue damage. Chronic hyperglycaemia also mediates overexpression and hyperactivity of nicotinamide adenine dinucleotide phosphate oxidases (NOX) 1, NOX2, NOX4, and NOX5.[26,27] These produce higher ROS levels, causing Ras-related C3 botulinum toxin substrate 1 and VEGF-mediated foot process effacement, p53-driven apoptosis, protein kinase C, and A disintegrin and metalloprotease 17-mediated mesangial

expansion, and uncoupling of nitric oxide synthase, causing vasocontraction.[26,27] This hypoxia also produces hypoxia inducible factor which, under hyperglycaemic state, becomes unstable,[28] and when chronically stimulated sparks a profibrotic effect.[29] Ultimately, this becomes a vicious cycle of inflammation, vascular injury, and further hypoxia.[28]

Role of Inflammation and the Complement System

DKD has multiple intersecting pathways propagating its disease process. Inflammation plays a vital role in the pathogenesis of DKD. Diabetes sets in motion various inflammatory cascades via oxidative stress, AGE, obesity, ischaemia, and damaged cells,[30] producing inflammatory molecules like NFκB, NLR family pyrin domain containing 3 (NLRP3)-linked caspases,[31] IL-1B, IL-6, and IL-18. This increase in AGE has been shown to be linked directly with increased expression of NLRP3-related proteins, which have been postulated to be mediators of chronic kidney disease,[31] with a role in activation of mesangial cells. NLRP3-related proteins are found in macrophages and inflammasomes and have been linked to multiple inflammatory disorders. In various mice models, attenuation of NLPR3 helped reduce chronic kidney disease (CKD) progression in a dose-dependent manner. Neutrophil and macrophage infiltration, lipoprotein oxidisation, and immune complex deposition can also occur.[6] With this ongoing inflammation there is increased production and deposition of amyloid A protein, which can also be used as a marker of disease progression.[32] CCR2 signalling distorts actin cytoskeleton and nephrin stability, damaging podocytes.[33] Hyperglycaemia-mediated promotion of elective cell simulated adhesion molecules cause tight junction abnormalities, resulting in proteinuria.[33]

Furthermore, the complement system activation has a huge impact on DKD progression. DKD progression has been linked to complement activation through mannose-binding lectins and ficolin-associated activation of the lectin pathway in the complement cascade. Hyperglycaemia leads to higher levels of glycan and galactosamine-bound substances that are recognised by these receptors.[34]

Genetic Modification

Hyperglycaemia and its effects cause DNA damage, and display effects of ageing in patients with diabetes by causing chromosomal telomere shortening,[35] resulting in proteinuria and DKD progression.[36] DNA damage activates various kinases, including ataxia-telangiectasia mutated and Rad3-related, followed by activation of p51 and p21. This inhibits cyclin-dependent kinase 2, impeding phosphorylation of retinoblastoma protein, which is essential for E2F transcription factor mediated DNA transcription. This inhibition of E2F transcription factor leads to permanent arrest of the cell cycle.[30]

Epigenetic changes constitute changes in genome function without change in DNA sequences. These are directly linked to lifestyle-directed exposures and individual encounters. In mice with diabetes, epigenetic changes have been noted as early as after 5 weeks of hyperglycaemia. DNA methylation, histone modification, and non-coding RNA are the main epigenetic changes.[37] Histone acetylation of HG3K9 causes increased expression of *AGT*, a component of RAAS system,[38] and hypomethylation of CpG islands (which are portions of some regulatory regions of genome) causes changes in the *Claudin-1* gene, resulting in more proteinuria.[39] H3K4me1 methylation promotes NFκB, non-coding RNA miRNA125b, prompting IL-6 and MCP-1 expression and miRNA-192-led TGF-β activity, plus collagen accumulation.[40] Hyperglycaemia also provokes activity of HDAC4, which deacetylates signal transducers and activators of transcription 1, inhibiting autophagic properties in podocytes.[41] Numerous other epigenetic changes play a role in promoting oxidative stress: e.g., hypomethylation of CpG or hyperacetylation of H3 histone precipitates *p66Shc* promotion, and lysine-specific histone demethylase 1 histone dimethyltransferase-driven inhibition of *SOD2*.[42]

Hypermethylation of klotho gene in both patients and mice with diabetes results in lower levels of klotho protein.[43] This decreases the favourable effects of klotho protein against ageing, oxidative stress calcification, and antifibrotic effect.[44,30]

Kidney Changes

The kidneys in a diabetic environment undergo many changes, from initial renal enlargement

to vasoconstriction, endothelial and tubular cell injury, to eventual renal fibrosis. The authors describe certain structural changes and their places in the pathogenesis of diabetic kidney below.

Glomerular Changes

The earliest changes in DKD are due to hyperfiltration in the glomerulus, causing thickening and stiffness of the glomerular basement membrane from sheer pressure[45] and deposition of extracellular matrix.[46] Secondly, mesangial expansion occurs due to leakage of protein, inflammation, and ongoing damaged tissue collection. This further disturbs the precision of glomerular filtration. Mesangiolysis leads to accumulation of matrix and cellular debris, which forms nodular structures named Kimmelstiel and Wilson nodules.[47] Additional mesangial destruction ends up in widespread glomerulosclerosis. Vascular changes with thickening of vessel walls and hyalinosis are also classic for DKD.

Podocyte Injury

Podocytes are the building blocks of the renal system. They are the prime managers of the filtration system. Podocyte injury has been shown to mimic diabetic changes even in absence of hyperglycaemia,[48] which indicates that podocyte injury is the key in development of DKD. Hyperglycaemia, oxidative stress, and inflammation leads to podocyte effacement, actin rearrangement, increased tight junction, slit diaphragm abnormalities, and apoptosis. In mice models, activation of mammalian target of rapamycin complex 1,[49] dynamin-related protein in mitochondria, nicotinamide adenine dinucleotide phosphate oxidase, and AMP-activated protein kinases[50] are responsible for these changes.

Cellular and Mitochondrial Injury

The renal tubules, given their high metabolic demand, are rich in mitochondria. Patients with diabetes have been noted to have mitochondrial abnormalities, including mitochondrial fragmentation, decreased adenosine triphosphate, increased mitochondrial permeability, and mitochondrial uncoupling as early as 4 weeks after hyperglycaemia.

Peroxisome proliferator-activated receptor-gamma coactivator-1α is amongst the prime regulators of mitochondrial synthesis, and its expression is altered in DKD.[51] The electron transport chain subunits in the mitochondria are also directly damaged by the oxidative stress that occurs with hyperglycaemia, leading to worsening mitochondrial metabolic functions[51] via DNA damage and decreased activity of glyceraldehyde 3-phosphate dehydrogenase. This leads to shifts in the glycolytic pathway to pylol and hexosamine pathways. Resultant oxidative stress causes decrease in AMP-activated protein kinase activity, leading to NFκB-mediated inflammation.[6]

Fibrosis

Unfortunately, all of the above mechanisms merge together and result ultimately in fibrosis and atrophic kidney tissue. The degree of tubulointerstitial fibrosis can even supersede glomerular lesions in determining renal function.[52] Local myofibroblasts, bone marrow-derived fibrocytes, and epithelial to mesenchymal transition as a response to the chemokines have been noted to produce this effect. Figure 2 shows some of these effects.

Target Therapies

Most of the pathway mediators that have been identified are potential targets to slow down DKD progression. Many of them have been tried and even more are in the pipeline. Table 1 summarises the ones mentioned below.

RAAS Blockade

angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers and aldosterone antagonists have been the mainstay for management of DKD for decades. Emerging evidence of nonsteroidal mineralocorticoid receptor antagonist, finerenone, is an exciting prospect as well.

Vitamin D supplementation has also been noted to decrease the levels of renin.[53]

Antihyperglycaemics

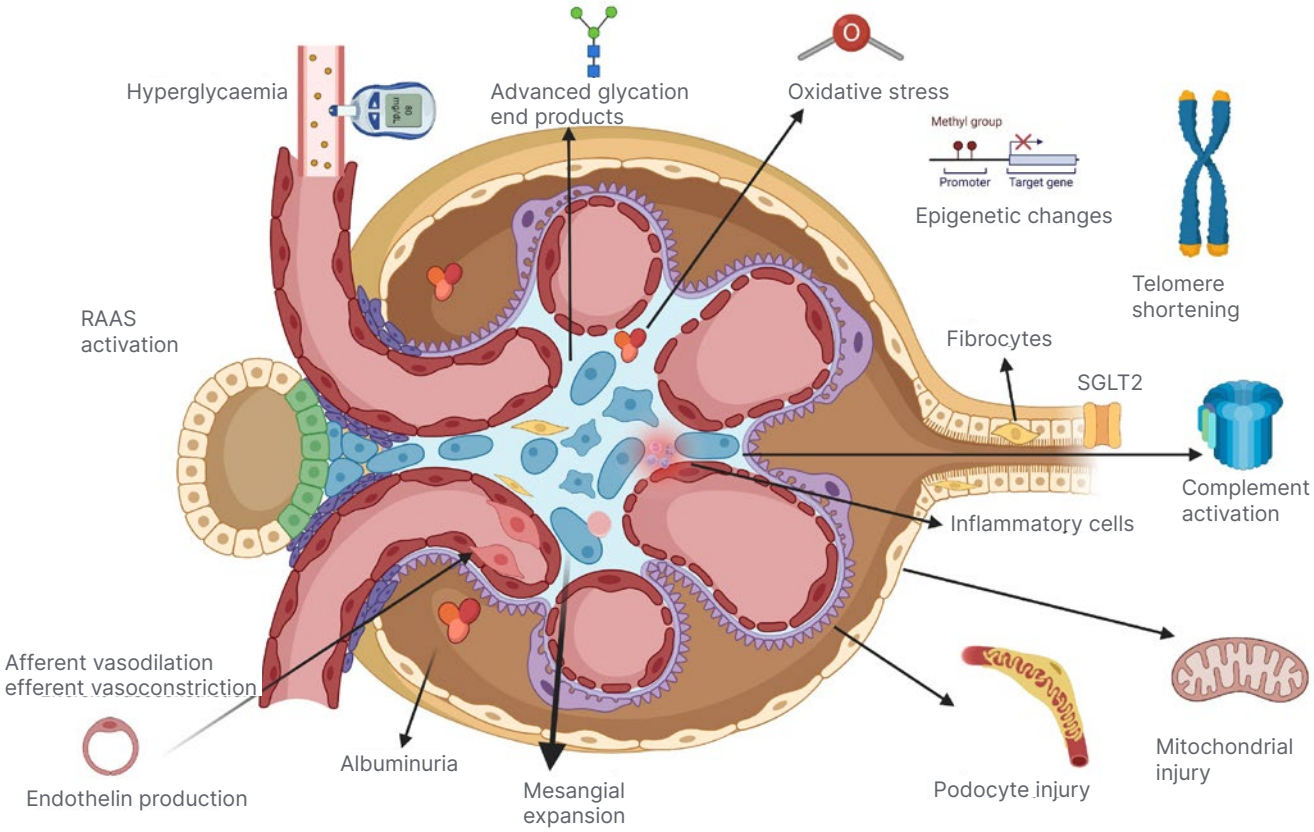
Hyperglycaemia is probably the instigator for all the downstream effects leading to DKD.

Table 1: Pathway mediators that have been identified as potential targets to slow down the progression of diabetic kidney disease.

Medication class	Published data	Unpublished or ongoing Trials
Antihyperglycemics	SGLT2 inhibitor, DPP inhibitor, GLP-1	N/A
RAAS blockade	ACE inhibitor/ARBs, aldosterone antagonist, finerenone	N/A
Vitamin D	N/A	Vitamin D supplements
AMPK activators	N/A	Metformin
Klotho	N/A	Klotho peptides
Antioxidants	N/A	Vitamin E supplements, pyridoxine, Mito Q
mTOR inhibitor	N/A	Sirolimus, everolimus
PKC inhibitor	Robuxistaurin	N/A
Nrf activator	Bardoxolome	N/A
ASK inhibitor	Selonsertib	N/A
JAK2 inhibitor	N/A	Baricitinib
CCL2 inhibitor	N/A	DMX–200, CCX140-B, emapticap
VEGF inhibitor	N/A	VEGF antibody
Glycoaminoglycan	Sulodeoxide	N/A
PDE2 inhibitor	Pentoxifylline	N/A
ETRa	Atrasentan	N/A
Antifibrotics	Antibody to TGF-β, CTGF	N/A
Complement inhibitors	N/A	Crinzyme, eculizumab, OMS721, anti-glycated CD59
Miscellaneous	N/A	VEGF inhibitor, PPARγ agonist, VAM inhibitor

ACE: angiotensin-converting enzyme inhibitor; AMPK: AMP-activated protein kinase; ARB: angiotensin receptor blockers; CCL2: chemokine (C-C motif) ligand 2; DPP: dipeptidyl peptidase; CTGF: connective tissue growth factor; ETRa: endothelin receptor antagonist; GLP-1: glucagon-like peptide-1; mTOR: mammalian target of rapamycin; N/A: not applicable; PKC: protein kinase C; RAAS: renin–angiotensin–aldosterone system; SGLT2: sodium–glucose co-transporter 2; VAM: vinyl acetate monomer; VEGF; vascular endothelial growth factor.

Figure 2: Depicts the glomerulus and tubular cells with some changes that happen in diabetes.



RAAS: renin–angiotensin–aldosterone system; SGLT2: sodium–glucose co-transporter 2.

Multiple medications have been in use to control diabetes. Particular attention has been received by some of the antihyperglycaemics for their renoprotective and cardioprotective effects than just lowering blood glucose.

- Glucagon-like peptide-1 analogues showed benefit in trials like SUSTAIN 6, REWIND, AWARD7, and AMOLITUDE-O. The FLOW trial is still ongoing.

- Dipeptidyl peptidase inhibitors showed benefit against albuminuria in MARLINA and CARMELINA trials.

- SGLT2 inhibitors have been the new breakthrough in DKD management in the last decade. Multiple studies have shown improvement in cardiac mortality, proteinuria, and prohibiting disease progression. CREDENCE and DAPA CKD have proven their utility in DKD. EMPA Kidney is the most recent trial investigating this, and is currently ongoing.

AMPK Activators

Metformin has been shown to activate AMPK levels, decreasing ROS production, and slowing DKD.[54]

Klotho Peptides

Klotho peptides is an anti-ageing protein which is found to have decreased levels in patients with diabetes. Its supplements have been hypothesised to help slow down the progression of DKD.[55]

Antioxidants

Oxidative stress and ROS are notorious for their injurious properties throughout the body. In DKD, multiple antioxidants have been shown to slow down the process. Vitamin E supplements,[56] pyridoxamine,[57] and mitoQ (in mice)[58] have been investigated.

mTOR Inhibitors

Rapamycin has been shown to slow down DKD progression in animal models; however, it has yet to go through human trials given its side effect profile.

Anti-inflammatory

Many inflammatory mediators have been targeted in hopes of slowing down the disease process. Some of them are mentioned below:

- Ruboxistaurin, a protein kinase C inhibitor, was noted to decrease albuminuria.
- Bardoxolone is an Nrf activator, with ongoing trials MERLIN and AYAME.
- Selonsertib is an ASK inhibitor undergoing MOSAIC trial.
- Baricitinib a JAK2 inhibitor, showed improvement in Phase 2 trials.
- Chemokine (C-C motif) ligand 2 or MCP-1 inhibitors DMX–200 and CCX140-B[59] and emapticap improves albuminuria.
- VEGF antibody trial undergoing recruitment.
- Sulodeoxide, a glycoaminoglycan composed of low molecular weight heparin, showed a decrease in albuminuria.[60]
- Pentoxifylline, a phosphodiesterase inhibitor, showed hopeful results in the PERIDIAN trial in 2015, with a larger trial ongoing.
- Atrasentan, an endothelin A receptor antagonist, showed promise in renal disease prevention (SONAR trial).
- Under trial: nicotinamide adenine dinucleotide phosphate antagonists, PPAR-Γ agonist, vascular adhesion molecules inhibitor.
- Anti–NLRP3 in rat models: Phenethyl isothiocyanate,[61] and naringin.[62]

Antifibrotics

Pirfenidone, an antibody against TGF-β and connective tissue growth factor was terminated due to side effects, but did reduce albuminuria. Some interest remains in minocycline, while N acetylcysteine did not show any positive outcomes.

Complement Inhibitors

Multiple complement inhibitors are being targeted in trials: C3a receptor and C5a receptor inhibitors, eculizumab, C-1 inhibitor (crinzyme) inhibits mannose-binding lectin due to structural similarity. OMS721 is an antibody against mannose-binding lectin associated serine protease 2. Anti-CD59 inhibits MAC.[63]

NOVEL APPROACHES TO EARLY DETECTION OF DIABETIC KIDNEY DISEASE

Despite their limitations, the authors have relied on creatinine-based eGFR calculation, urine albumin, and creatinine excretion ratios as tools of detection and progression of DKD. Combining cystatin C and creatinine-based eGFR calculation has improved estimation of kidney function, but still does not help in earlier detection of the disease. In recent years, due to advancements in the fields of metabolomics, transcriptomics, and bioinformatic analysis, it has been possible to detect earlier changes, given better understanding of the components in the pathophysiology of DKD, which has become an alternative to estimate kidney function due to inaccuracies of eGFR. Neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 showed a role in detecting glomerular hyperfiltration.[64] Development of DKD can be predicted with urinary levels of N-acetyl-β-D-glucosaminidase and 8-oxodG.[64] Urinary levels of pentosidine[65] and serum levels of tissue necrosis factor receptors[66] were predictive of progression of albuminuria and DKD, respectively. DNA 65 (a panel with fragments of collagen 1)[67] and CKD 273 (a set of 273 urinary peptides)[68] helped to distinguish and detect DKD earlier. Other metabolomic studies have

shown various changes in metabolite levels that can indicate DKD earlier. These metabolites are from metabolic pathways involving fatty acids, phospholipid oxidation, urea cycle, and amino acid metabolism, to name a few.[69] Some of the indicative metabolites that are increased in DKD include aspartic acid, citruline, symmetric dimethylargine, and kynurenine.[69] Levels of uremic solutes, fatty acids, amino acids, histidine, butenoylcarnitines, acyl carnitines, and branched chain fatty acids were able to predict progression of DKD years in advance.[69] A recent comparison of 232 patients with 100 healthy individuals showed that certain metabolomic markers, like dodecanoylcarnitines, triglylcarnitine, and isovalerylcarnitine, strongly predicted albumin creatinine ratio.[70]

CONCLUSION

We have come a long way in discovering the mechanics behind the destructive pathology of DKD, but there still remains a lot of work to be done. The unpredictability in the disease course of DKD, due to its nonlinear pattern of eGFR decline,[71,72] indicates the variety of factors affecting its pathogenesis. We now have a better picture of how high glucose levels involve haemodynamic changes, changes in hormone production, metabolic pathway alteration, oxidative stress, and worsening inflammation. It is clear how diabetes not only involves the podocytes and the glomeruli, but also damages the tubules. The damage caused is so widespread that it involves changes on the cellular level, including mitochondrial injury and epigenetic changes. Understanding DKD at a molecular level helps with the ability to tailor management, as we try to prevent ESKD or complications of DKD.

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SGLT2 Inhibitors for Nephrologists

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Abstract

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are the mainstay of therapy for the prevention of progressive renal damage in diabetic and non-diabetic kidney diseases, especially glomerulonephritides. Sodium-glucose co-transporter-2 inhibitors are a relatively new class of oral antidiabetic drugs. Early evidence suggests that there are renal and cardiovascular benefits of this class of drugs that extend beyond glycaemic control for patients both with and without diabetes. With each and every trial, the limit for the glomerular filtration rate has been set lower, making the drugs more suitable from the perspective of nephrologists. This drug class has the potential to become the mainstay of reno-protective strategies used by nephrologists, in addition to angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. This article reviews the evidence and reports that are already published regarding the use of sodium-glucose co-transporter-2 inhibitors to treat non-diabetic glomerular disease.

Key Points

1. Early evidence for the antidiabetic sodium-glucose co-transporter-2 inhibitors (SGLT2i) suggests that there are renal and cardiovascular benefits of this class of drugs that extend beyond glycaemic control for patients both with and without diabetes.

2. Recent studies have shown benefits of SGLT2i in patient groups with lower GFR cut-offs (>25 mL/min), in both diabetic nephropathy and non-diabetic proteinuric primary renal diseases.

3. Anticipated upcoming studies consider the effect of SGLT2i in patient groups with GFR >20 mL/min, and in non-proteinuric primary renal diseases, as this drug class may become a mainstay in management and prevention in primary renal diseases beyond the scope of diabetic nephropathy.

SGLT2 INHIBITORS FOR NEPHROLOGISTS

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers are the mainstay of nephroprotective strategies both for diabetic and non-diabetic renal diseases. Nephrologists are in search of novel therapeutic modalities that can positively affect the progressive course of renal diseases and decline in glomerular filtration rate (GFR). Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are a newer class of oral hypoglycaemic drugs that was initially developed to treat patients with diabetes. The mechanism of action of SGLT2i involves the inhibition of the absorption of glucose in the proximal tubular cells, thereby inducing glycosuria and a reduction in plasma glucose levels. There is early evidence regarding the renoprotective and cardioprotective properties of SGLT2i beyond glycaemic control.[1,2] This article presents the existing evidence regarding the role of SGLT2i from a nephrologist's perspective.

Initial trials conducted on SGLT2i had cardiac primary endpoints and demonstrated beneficial effects, not only on the cardiovascular system but also on the renal system, as secondary endpoints. Major trials in this regard are summarised here.

In 2015, the EMPA-REG OUTCOME trial was published. This randomised trial included patients with Type 2 diabetes who had a GFR of 60–90 mL/min. The primary end-points of cardiovascular mortality, all-cause mortality, myocardial infarctions, and strokes were all shown to be reduced in the treatment arm compared with the placebo. Patients managed on empagliflozin were also shown to have reduced rates of renal dysfunction, progressive renal impairment, and worsening albuminuria as secondary outcomes.[3]

The CANVAS trial, published in 2017, was similarly based on cardiovascular primary endpoints such as strokes, myocardial infarctions, and cardiac deaths in patients with Type 2 diabetes and a GFR ranging from 60–90 mL/min. Outcomes related to kidneys, such as reduction in albuminuria, and a composite renal outcome of a reduction in GFR, dialysis, and death from renal failure, were secondary in nature. Both primary and secondary outcomes were reduced in the canagliflozin arm in comparison with the placebo.[4]

The DECLARE–TIMI trial, published in 2019, was a randomised controlled trial (RCT) that compared dapagliflozin with a placebo. This trial studied major adverse cardiovascular events, cardiovascular death, and hospitalisation as primary end-points in patients with Type 2 diabetes and a GFR ranging between 60–90 mL/min. Effects on the kidneys were studied as a secondary composite outcome of: decrease in estimated GFR (eGFR) of >40%, new end-stage renal disease (ESRD), and death from renal causes. Dapagliflozin decreased cardiovascular deaths and heart failure-associated hospitalisations, but not major adverse cardiovascular events. Renal composite outcomes were also lower in the dapagliflozin group when compared with a placebo.[5]

The DAPA-HF trial included patients with Type 2 diabetes with a lower GFR cut-off of >30 mL/min. Its composite primary outcome was worsening heart failure and cardiovascular death, while the secondary composite renal outcome was a decline in GFR of >50%, ESRD, dialysis, or transplantation. This trial showed a significant improvement in the primary cardiovascular outcome in the intervention arm compared with the placebo group; however, the secondary composite renal outcome was similar in both groups.[6]

The EMPEROR-Reduced (ejection fraction: <40%) and EMPEROR-Preserved (ejection fraction: >40%) trials suggested the renoprotective effects of SGLT2i in patients with reduced, but not preserved, cardiac function, although cardiac outcomes were improved in both trials.[7,8]

Subsequent trials were primarily conducted with renal primary endpoints. The first of these was the CREDENCE study, a placebo-controlled RCT that was published in 2019. Baseline characteristics of included patients were: Type 2 diabetes, a urine albumin-to-creatinine ratio (ACR) of >300 mg/g, and a GFR of 30–90 mL/min. The primary renal endpoints in this trial included renal or cardiovascular

deaths, doubling of creatinine, and ESRD. The trial was stopped before study completion as a significant improvement was demonstrated in the doubling of creatinine and in ESRD, the primary outcomes.[9]

The DAPA-CKD trial was published in 2020. This RCT included 4,304 patients with baseline characteristics of an even lower GFR of 25–75 mL/min and a urine ACR of 200–5,000 mg/g. This trial was the first to include patients without diabetes as well as patients with diabetes. The patients who were not diabetic were mostly comprised of patients with proteinuric nephropathies, such as hypertensive nephropathy (16%), IgA nephropathy (6%), and focal segmental glomerulosclerosis (FSGS; 3%). Notably, patients with polycystic kidney disease, lupus nephritis, vasculitis, and Type 1 diabetes were excluded from this study.

Patients were randomised to receive either dapagliflozin or a placebo, while a majority were maintained on ACEi (97%). Primary outcome measures included renal endpoints, such as a 50% decline in renal function (measured by the GFR), end-stage renal disease, and renal or cardiovascular death. This trial was stopped prematurely as it demonstrated the beneficial effects of dapagliflozin on the primary outcome: 9.2% in dapagliflozin versus 14.9% in the placebo arm (hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.51–0.72; p<0.001). The renal benefits were similar between patients with or without diabetes, patients with a GFR of < or >45 mL/min, and patients with albuminuria < or >1000 mg/g.[10,11]

The DIAMOND was a double-blind, randomised, placebo-controlled trial with a crossover design that was published in 2020. It included 53 adult patients (mean age: 51 years) with proteinuric renal disease (proteinuria: 500–3,500 mg/24 hours; mean baseline proteinuria: 1,110 mg/24 hours) and decreased renal function (GFR: >25.0 mL/min; baseline mean GFR: 58.3 mL/min). The study included patients with IgA nephropathy, FSGS, hypertensive nephropathy, and other pathologies. All patients had stable renin–angiotensin–aldosterone system blockade. In this trial, dapagliflozin (10 mg) was compared with a placebo in a crossover fashion, with a treatment period lasting for 6 weeks. There was no statistically significant difference in proteinuria reduction between the two groups. Systolic and diastolic blood pressure also did not differ between the two groups. The dapagliflozin arm showed a significant reduction in GFR (−6.6 mL/min) compared with the placebo group, which was reversible with drug discontinuation. The adverse events were also similar between the two groups. This trial concluded that, in contrast with previous evidence, dapagliflozin did not reduce proteinuria in patients with non-diabetic chronic kidney disease (CKD), emphasising the lack of understanding of this fascinating drug class and the need for further studies.[12]

Evidence of the benefit of SGLT2i in primary renal, non-diabetic kidney diseases is emerging in the form of small case reports. A summary of these findings is presented here.

In a case series of six patients with hereditary FSGS (*NPHS2* and *INF2* mutations) and X-linked Alport syndrome, the addition of SGLT2i to ACEi was shown to reduce proteinuria by 40%, while GFR stabilised after an early decline.[13] In a small case series, which included nine patients (mean age: 10.4 years) with both proteinuric glomerulopathy (including five patients with Alport syndrome) and normal renal function (GFR: 104.9 mL/min), dapagliflozin was used in addition to fosinopril. The authors reported a proteinuria reduction of 33% and 22% at 4 and 12 weeks, respectively.[14] Other studies have produced negative results for SGLT2i when used in patients with FSGS. In a small study conducted on humans and rodents, dapagliflozin was not found to induce changes in GFR or proteinuria in patients with FSGS after 8 weeks of therapy.[15] Dapagliflozin did not reduce proteinuria in the 11 patients with FSGS that were included in the DIAMOND study mentioned above.[16] For 104 patients with FSGS that were included in the DAPA-CKD study, the rate of chronic decline of GFR was lower in the dapagliflozin arm compared with a placebo.[17]

The DAPA-CKD trial included 270 patients with IgA nephropathy. Nearly half of patients were either randomised to dapagliflozin or a placebo and followed for up to 2 years. The mean eGFR was 43.8±12.2 mL/min/1.73m^2. The mean urinary ACR was 900 mg/g. Primary renal and cardiac composite outcomes were significantly

reduced in the dapagliflozin arm compared with the placebo arm (4% versus 15%; HR: 0.29; 95% CI: 0.12–0.73; p=0.005), including for ESRD (4% versus 12%; HR: 0.30; 95% CI: 0.11–0.83; p=0.014), eGFR decline (−3.5 versus −4.7 mL/min/1.73m^2/year, respectively; 95% CI: −0.12–2.51), and ACR decline (26% in dapagliflozin arm; 95% CI: −0.37, −14.00; p<0.001). Adverse events, including hypoglycaemic episodes and ketoacidosis, were similar between the two groups.[18,19] However, nearly 14% of patients with IgA nephropathy also had diabetes mellitus, and the analysis lacks information regarding the optimisation of ACEi doses in these patients, necessitating further studies.[20]

POSSIBLE MECHANISMS OF RENAL PROTECTION BY SGLT2 INHIBITORS

Normally, glycosuria appears when blood glucose levels exceed the 180 mg/dL threshold.[21] Hyperglycaemia with an increased intrarenal synthesis of angiotensin II promotes increased proximal tubule SGLT2 expression. This in turn contributes to an increase in tubular glucose reabsorption, with an increase in the threshold of glycosuria to 200–240 mg/dL, as seen in patients with diabetes.[22] In diabetes, higher proximal tubule sodium reabsorption due to increased SGLT2 expression reduces the delivery of sodium to the macula densa, which in turn activates tubuloglomerular feedback, ultimately causing afferent arteriolar vasodilation, increased intraglomerular pressure, and glomerular hyperfiltration.[23,24] This glomerular hyperfiltration is considered to be one of the major factors responsible for progressive renal damage in both diabetic and non-diabetic renal diseases. SGLT2i block proximal tubular sodium reabsorption, increasing distal sodium delivery, thereby acting to reduce the intraglomerular pressure, which prevents renal damage caused by hyperfiltration injury.[25]

Other mechanisms include: anti-inflammatory and antifibrotic effects by suppressing reactive oxygen species and inhibiting inflammatory and fibrotic mediators; increased sensitivity of muscles to insulin (counter to insulin resistance associated with uraemia and acidosis); blood pressure reduction, possibly through diuretic and natriuretic effects; possible action on the intrarenal renin-angiotensin system; direct effects of SGLT2i receptors on endothelial and mesangial cells; inhibition of epithelial–mesenchymal transformation; and reduction of uric acid levels.[26-33] Studies have also shown improvements in histological changes, such as glomerular capillary dilatation, mesangial expansion, glomerular adhesions to Bowman's capsule, preservation of the podocyte foot process ultrastructure, and prevention of podocyte depletion.[34]

Considering the early benefits of SGLT2i, even in patients with non-diabetic CKD, these agents may have a place in the treatment of patients with CKD in the future. While SGLT2i may not affect the primary inciting injury, these agents may have an impact on glomerular hyperfiltration and interstitial fibrosis, which are the final pathways of progressive renal damage.

The EMPA-KIDNEY trial is currently undergoing and includes patients with CKD and with a lower GFR cut-off limit of 20 mL/min/1.73 m^2.[35] This trial is expected to shed more light on the renoprotective effects of SGLT2i in patients with CKD who have a primary renal disease independent of diabetes.[36]

CONCLUSION

SGLT2i are a relatively new class of oral hypoglycaemic agents. Multiple trials have suggested the renoprotective properties of these agents in patients with diabetic nephropathy, as well as non-diabetic proteinuric primary renal diseases. Studies conducted with primary cardiac endpoints had a GFR cut-off of more than 60 mL/min. Later, primary renal studies attempted to reduce the cut-off to 25 mL/min, making a case for use of these agents in relatively advanced renal impairment. The ongoing EMPA-KIDNEY trial has further reduced the GFR cut-off to 20 mL/min, and, depending on the results of this trial, SGLT2i may also find a role in the management of patients with advanced renal impairment.

All of the previous trials focused on the renal benefits of SGLT2i in proteinuric renal diseases. The EMPA-KIDNEY trial will also clarify the role of SGLT2i in non-proteinuric primary renal

diseases. Nephrologists eagerly await the results of this study, which could add SGLT2i to the armamentarium of agents used to prevent progressive primary renal diseases. New research is expected to shed more light on novel indications for this newer class of agents; the preliminary results are encouraging, especially in patients with IgA nephropathy and Alport syndrome. Nephrologists throughout the world await further studies and new data regarding use of SGLT2i in primary renal diseases beyond the scope of diabetic nephropathy.

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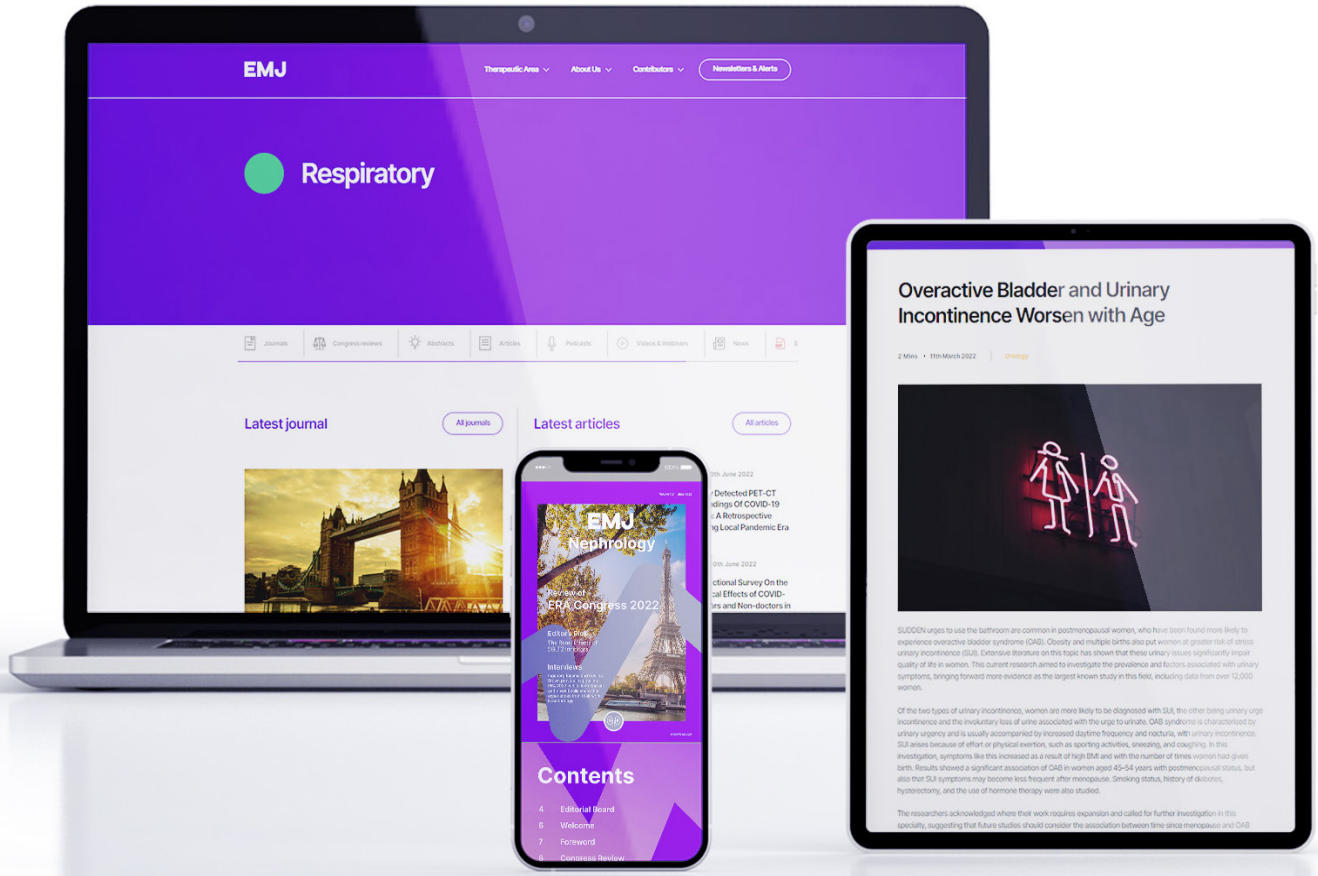

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