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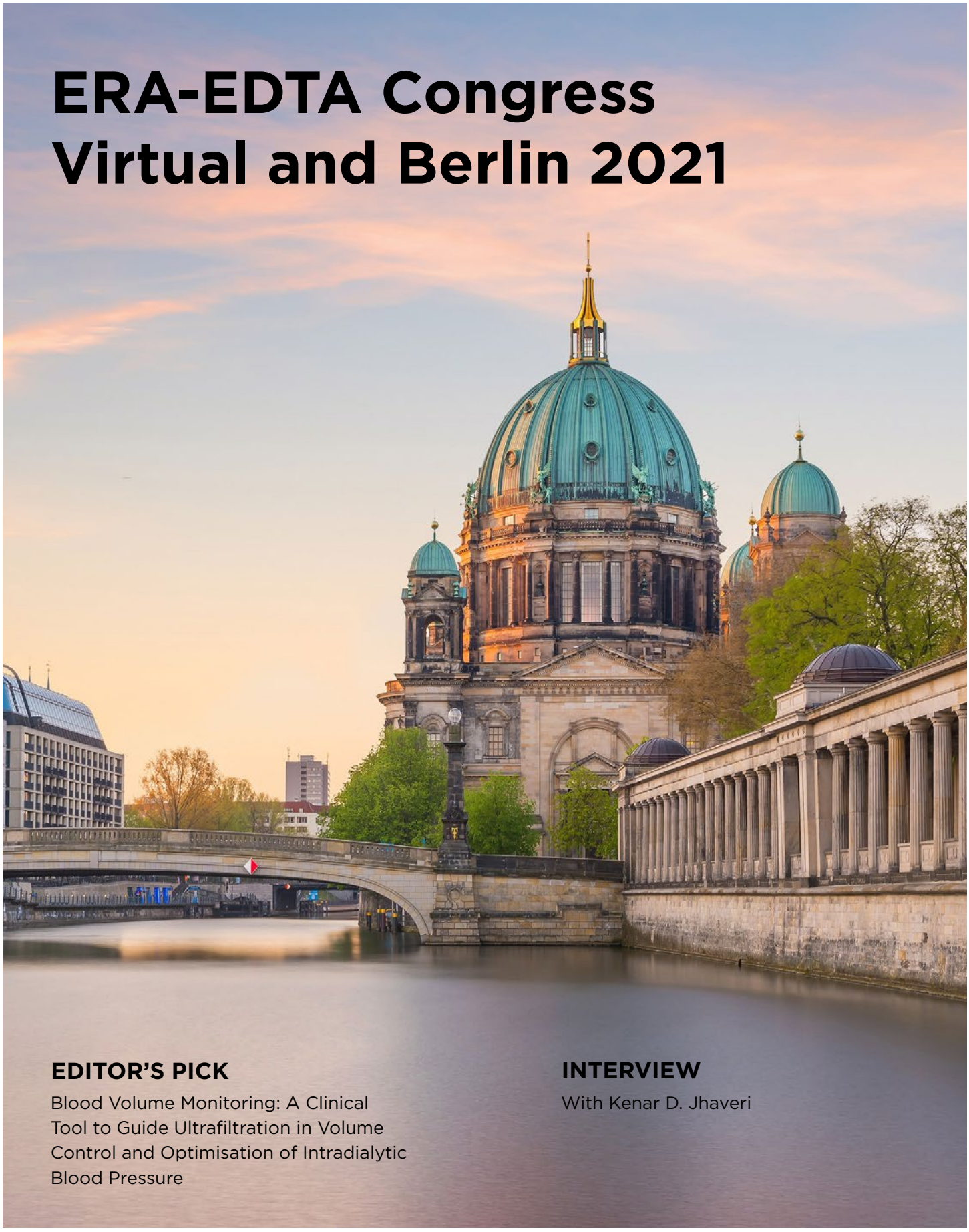
ERA-EDTA Congress Virtual and Berlin 2021



EDITOR'S PICK

Blood Volume Monitoring: A Clinical Tool to Guide Ultrafiltration in Volume Control and Optimisation of Intradialytic Blood Pressure

INTERVIEW

With Kenar D. Jhaveri

Contents

"This eJournal explores novel and insightful developments in nephrology through a series of captivating interviews, abstracts summaries and peer reviewed articles from experts within the field."

Spencer Gore, CEO

Editorial Board

VIEW IN FULL ←

Aims and Scope

EMJ is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

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Front cover and contents photograph: Berlin, Germany, home of the ERA-EDTA 2021. © f11photo / 123rf.com

EMJ Nephrology 9.1

Welcome

Dear Readers,

We would like to welcome you to this issue of *EMJ Nephrology*. Prepare yourselves for a journal packed with the latest nephrology updates, including peer-reviewed articles and exclusive interviews with experts in the field. We are excited to share with you an in-depth review from the incredible European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Virtual Congress 2021, as well as a broad range of abstract summaries of the research presented.

In this eJournal, we are proud to present peer-reviewed articles on topics including non-coding microRNA-223 proving to be a promising biomarker of chronic kidney disease, the causes of hypermagnesaemia, and blood volume monitoring as a tool to guide ultrafiltration. The Editor's Pick for this issue is 'Blood Volume Monitoring: A Clinical Tool to Guide Ultrafiltration in Volume Control and Optimisation of Intradialytic Blood Pressure' by Mahony and Ward. This fascinating review article examines the current evidence to support the use of blood volume monitoring to prevent intradialytic hypotension events and assess dry weight. Read on for an interview with Kenar Jhaveri about his ongoing passion for nephrology, his current research, and innovation within the discipline, alongside highlights in COVID-19-related acute kidney disease.

For those who were unable to attend, please enjoy a comprehensive review of the incredible ERA-EDTA Virtual Congress 2021; despite the virtual format, the congress was seamlessly executed with >1,000 expert speakers, a comprehensive scientific programme, and the most recent, hot-topic nephrology research. We had the pleasure of carrying out interviews with Robert John Unwin, Scientific Advisory Board member of ERA-EDTA, and Peter Blankestijn, Council member of ERA-EDTA. Be sure to read our summaries of stand-out abstracts from the congress, written by the authors themselves, on topics including nephrotoxic mechanisms of gadolinium, spontaneous renal artery dissection, senescence-like changes in B-cell phenotype in patients with haemodialysis, and more.

I would like to take this opportunity to thank the Editorial Board, authors, clinicians, experts, and the EMJ publishing team for their hard work in bringing this research to you. We hope that *EMJ Nephrology*, and future publications, will inspire new research ideas to contribute to advancements in the field.

Spencer Gore

Chief Executive Officer, EMG-Health

In Memory of Donal J. O'Donoghue OBE (1956–2021)

Consultant Renal Physician, Salford Royal NHS Foundation Trust, Professor of Renal Medicine, University of Manchester, UK

We would like to take this opportunity to fondly remember Donal J. O'Donoghue, a valued member of the editorial board of *EMJ Nephrology*. He was a respected nephrologist, researcher, and an inspiration to the renal community at large. Having qualified in physiology and medicine in Manchester, UK, and trained in internal medicine and nephrology in the England, France, and Scotland, his influence within the nephrology community was extensive. O'Donoghue became a consultant renal physician in 1992 and had previously served as the inaugural President of British Renal Society, the Renal Association, and a Registrar of the Royal College of Physicians (RCP), London, UK.

We had the pleasure of working alongside O'Donoghue since 2017 when he joined EMJ as an editorial board member. He was exceptionally important within the kidney community and spent over 30 years devoting work to enhancing the care of patients diagnosed with kidney disease. He was the Chair of the patient support charity Kidney Care UK and the first National Clinical Director of Kidney Care at the Department of Health. Due to his passion and dedication in his profession, he was awarded an Order of the British Empire (OBE) in 2018 for his services to patients with kidney diseases.

The RCP President Andrew Goddard tributed O'Donoghue: "Words cannot express how sad this has made all of us at the RCP. Donal was the loveliest person and considered by many to be the 'big daddy' of British renal medicine. He was my friend, my wingman, and my confidant. I will miss him terribly."

O'Donoghue died peacefully at the critical care unit of Stepping Hill Hospital, Stockport, UK, on 3rd January 2021 with COVID-19. He will be greatly missed by the wider nephrology community. Our thoughts go out to his family and colleagues.

Foreword

Dear Readers,

Firstly, I would like to thank all authors, peer reviewers, and Editorial Board members for their commitment and dedication to this issue of *EMJ Nephrology*. The COVID-19 pandemic and associated kidney complications have involved our colleagues in a yet-undefeated battle. Last year, one article of the journal addressed this aspect.

This issue of *EMJ Nephrology* includes original studies and reviews covering many fields of kidney disease, ranging from the pathogenesis of chronic kidney disease and acute kidney failure to the role of blood volume monitoring in patients on dialysis.

The Editor's Pick for this publication is the article by Mahony and Ward on blood volume monitoring in patients on dialysis, titled: 'Blood Volume Monitoring: A Clinical Tool to Guide Ultrafiltration in Volume Control and Optimisation of Intradialytic Blood Pressure.' Although several studies have been carried out in this area, it is still a major factor of morbidity among patients on dialysis. Finding a real-time calculation of changes in relative blood volume via a cuvette located in the arterial blood line would be of great help in improving blood volume and ultrafiltration rate.

The study on trace elements and their relationship with chronic kidney disease is also interesting, and the finding that strontium (an important calcium-mimicking sensor) is associated with a reduced glomerular filtration rate is of the utmost importance.

Similarly, in a different study, non-coding micro-RNA has been identified as a biomarker of chronic kidney disease.

Acute kidney injury in critical care patients is a frequent cause of death. The finding of the role of dexmedetomidine in these patients is therefore extremely important.

Finally, a review article on the causes of hypermagnesaemia adds interest to this important electrolyte.

A full review of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Virtual Congress 2021 is offered if you would like to be reminded of the success of the ERA-EDTA's 58th Congress.

I hope you find interest in this issue of *EMJ Nephrology*, and that you are keeping safe and well.

Maurizio Salvadori

Professor of Nephrology, Renal Unit, Department of Renal Transplantation, Careggi University Hospital of Florence, Italy

Available now.

EMJ 6.2

Symposium Review

Pioneering Best Practices in Atopic Dermatitis: Results from the Quality-of-Care Initiative

Poster Review

Late-Breaking Abstracts: Health Status Benefits of Mavacamten in Obstructive Hypertrophic Cardiomyopathy and the Modifying Effect of Ejection Fraction on the Therapeutic Benefit of Omecamtiv Mecarbil in Heart Failure

Articles

Editor's Pick: Relating Ventilatory Support and Drug Treatment Strategies to the Fundamental Pathophysiology in COVID-19 Illness

Understanding the Impact of Non-Dystrophic Myotonia on Patients and Caregivers: Results from a Burden of Disease Healthcare Survey

Oxy-hydrogen Gas: The Rationale Behind Its Use as a Novel and Sustainable Treatment for COVID-19 and Other Respiratory Diseases

Prevalence of Scoliosis in Hypermobile Ehlers-Danlos Syndrome

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Congress Review

Review of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Virtual Congress 2021

Location: ERA-EDTA 2021 Congress

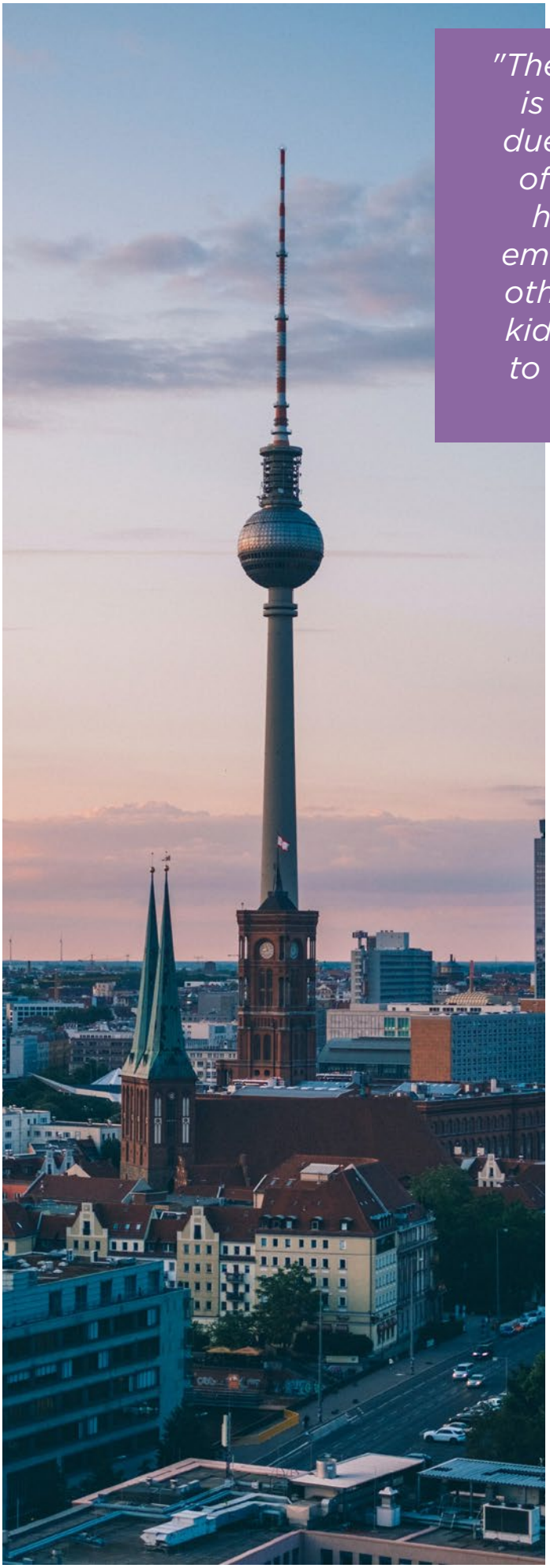
Date: 5-8th June 2021

Citation: EMJ Nephrol. 2021;9[1]:12-23. Congress Review.

BERLIN, the modern architectural capital city of Germany hosted this year's ERA-EDTA Congress that took place on 5-8th June 2021. Albert Einstein, one of the greatest theoretical physicists in history, lived and carried out his experimental work in Berlin, Germany for 22 years. It was during his time in this city that he was awarded the Nobel Prize in physics in 1922. It comes as no surprise that the municipality has attracted so many more scientific researchers and associations, each one attempting to soak in the aura of one of the most prominent minds in history.

Global challenges of the COVID-19 pandemic meant that not everyone was able to attend the ERA-EDTA Congress 2021 in person. However, a select few vaccinated nephrologists were able to make the occasion. The momentum of the 58th meeting was unstirred, as this is the second virtual meeting hosted by the society. The ERA-EDTA President Christoph Wanner, in the opening ceremony, assured the participants that the society was adapting to the changing times of working and networking remotely, it was a real renewal process, refurbished, resilient, and stronger than ever before.

The benefits of a virtual hybrid congress were clear to all the attendees and presenters as they gathered in their homes, offices, and even laboratories to observe the online platform come to life. Over 5,207 attendees were spoiled for choice with 1,159 speakers who presented 107 sessions, 1,056 mini-orals, 58 sponsors and exhibitors, and Center for Executive and Professional Development (CEPD) courses. The Congress President, Markus Ketteler, Head of Division of Nephrology, University Hospital Würzburg, Germany, during the opening ceremony took the opportunity to thank the Scientific Committee Chair Giovambattista Capasso, Director Department of Translational Medical Sciences, University Luigi Vanvitelli Naples, Italy who laboured tirelessly to provide the innovative ground-breaking science programme. With over 2,000 high-quality



"The culture of mechanistic thinking is shared by many nephrologists due to the in-depth understanding of the physiology of the kidneys, heart, and even the brain. With emerging rare kidney diseases and other ailments associated with the kidney, education is key to stay up to date with recent developments within the field"

abstracts submitted and 1,191 accepted this year, Ketteler acknowledged Maria José Soler Romeo, Chair of the Paper Selection Committee, Giuseppe Palladino, ERA-EDTA Research and Development Manager, researchers and dedicated volunteers and researchers for their contributions, implementation, collaboration, and submissions for the engendered execution of a successful ERA-EDTA meeting.

The culture of mechanistic thinking is shared by many nephrologists due to the in-depth physiology of the kidneys, heart, and even the brain. With emerging rare kidney diseases, education is key to stay up to date with recent developments within the field. On the first day of the congress, several educational topics were covered: hypertension, diabetes and cardiovascular diseases in chronic kidney disease, recurrent glomerulonephritis following renal transplantation, nephropathology of COVID-19, and so much more. Wanner encouraged nephrologists to expand their expertise and broaden their knowledge in various aspects of internal medicine, especially the next generation of doctors.

Appreciation is a key motivator, and in ERA-EDTA honorary awards were distributed as an acknowledgement for service by society Wanner. The first two awards were presented to the 2021 Congress President Ketteler, as recognition for his professionalism in the organisation of this year's virtual congress, and Capasso, Scientific Committee Chair, for his service in the society for the past 2 years and collating the scientific programme of this congress. Additionally, other

"See you in Paris in 2022 for the 59th ERA-EDTA meeting"

awards were presented covering three categories: David Jayne, University of Cambridge, UK for outstanding clinical contributions to nephrology; Juan Jesus Carrero, Department of Epidemiology, Karolinska Institutet, Solna, Sweden for research excellence in nephrology; and Thimoteus Speer, Translational Cardio-Renal Medicine, Saarland University Hospital, Homburg, Germany, who received the Stanley Shaldon award for young investigators.

It was clear that climate change and its effects on health was a hot topic in this year's congress. During the Welcome Ceremony, a lecture was presented by Carlo Barbante, Director of the Institute of Polar Sciences, Ca'Foscari University of Venice, Italy, who discussed climate change, global warming, and the environmental impact of these changes in the present and future projections. In this issue of *EMJ Nephrology*, our team covered a session review of climate change and nephrology and a selection of other topics from the ERA-EDTA Congress, aiming to impart some of the knowledge shared at the congress.

Networking and building rapports are essential within the nephrology community, where researchers and professionals with different specialisations in nephrology can meet face to face to share ideas and information on the latest research and knowledge. "See you in Paris in 2022 for the 59th ERA-EDTA meeting," President Wanner, shared. ■

ERT-EDTA 2021 REVIEWED →

"The ERA-EDTA was one of the first international medical societies to urge investment in the transformation to a greener healthcare. The theme of this year's fully virtual Congress, Healthy Environment, Healthy Kidneys, underlines the ERA-EDTA's commitment and the important role of nephrologists in addressing climate change."

'Healthy Environment, Healthy Kidneys': The ERA-EDTA Position on Climate Change and Health

CLIMATE change poses one of the most significant risks to human health, with 24% of deaths worldwide attributable to environmental factors. The burden of addressing the mortality and morbidity associated with climate change, such as undernutrition, mental disorders, and noncommunicable diseases (e.g., chronic kidney disease and acute kidney injury), falls to nephrologists and other healthcare professionals. Despite this, the healthcare sector is believed to produce 4.4% of the global carbon footprint, greatly exacerbating the climate emergency.

Therefore, 'Healthy Environment, Healthy Kidneys' was chosen as the theme for this year's ERA-EDTA Virtual Congress, 5th–8th June 2021. This highlighted the vital role played by healthcare professionals in advocating for international efforts to reduce greenhouse gas emissions and protect against future global warming.

According to ERA-EDTA President Christopher Wanner: "The ERA-EDTA was one of the first international medical societies to urge investment in the transformation to a greener healthcare. The theme of this year's fully virtual Congress, Healthy Environment, Healthy Kidneys, underlines the ERA-EDTA's commitment and the important role of nephrologists in addressing climate change."

On Day 3 of the ERA-EDTA Congress, a symposium titled 'Climate change and health: the opinion of the younger generation' provided an opportunity for younger healthcare professionals to share their views on climate change and health. Martin Herrmann and Sylvia Hartmann, President and Vice Chair of the German Alliance for Climate Change and Health, respectively, were two of the speakers. Herrmann discussed the threat of climate change to the public health achievements of the last century, and noted that there is a major opportunity in addressing climate change, since climate protection strategies are linked with substantial health benefits. Similarly, Hartmann considered the perspectives of the coming medical generation on the climate crisis. Beyond daily medical routines, healthcare professionals have a unique responsibility to demonstrate the health emergency caused by climate change.

Warner concluded: "Throughout the world younger people are in the vanguard of action against global warming, and have shown us that addressing climate change is everyone's responsibility." ■

COVID-19 Causing Long-Lasting Renal Problems?

CONCERNING evidence has emerged from on ERA-EDTA 2021 that took place on 5–8th June, describing molecular tissue damage caused by the novel coronavirus leading to long-lasting kidney issues. This information has spurred nephrologists to stress the importance of aftercare following COVID-19 infection, and acknowledge the strong predictive potential for severity which lies with using kidney values early in the course of disease onset.

Associated nephritis has been identified as an early warning signal for serious courses of the virus, and at ERA-EDTA the findings were presented from study by Oliver Gross, who led a research team to investigate prediction strategies. Crucially, kidney involvement with the virus is an important risk factor for mortality; early complications such as proteinuria, hypoproteinemia and anti-thrombin III deficiency are described as having prognostic potential, building on prior knowledge that acute kidney injury (AKI) was contributing to this relationship.

Two hundred and twenty-three patients were included, with 145 used as a predictive cohort; utilising test strips to indicate early urinary changes and therefore a more severe COVID-19 course, study endpoints were ICU admission or mortality. Gross explained at the opening press conference for ERA-EDTA, "kidney values are a seismograph for the course of COVID-19 disease," talking about combining urine and serum markers as a predictive system.

Other studies were mentioned, and support the association with kidney involvement, concluding dramatically worsened outcomes of viral disease and increased mortality. A Chinese study found 1.25% of patients died without kidney involvement, compared with 11.2% mortality in those with.

"The kidney must be at the centre of COVID-19 aftercare," was the statement Gross gave, going on to mention, "early treatment can halt the loss of kidney function".

Questions raised surround the specific long-term impacts expected after COVID-19, particularly when many patients never recover kidney function, and instead see gradual deterioration over the course of the disease. "The kidney must be at the centre of COVID-19 aftercare," was the statement Gross gave, going on to mention, "early treatment can halt the loss of kidney function." He delivered an important conclusion, which will focus clinical action; "Given that kidney disease does not produce symptoms until very late, we would like to make people who have had COVID-19 disease aware of the possibility of long-term consequences on the kidneys. It's important that general practitioners check their patients' kidney values (GFR, albuminuria) on a regular basis.". ■

Iptacopan an Exciting Alternative Treatment for IgA Nephropathy

HINDERING the lives of countless teens, IGA nephropathy (IgAN) is a chronic kidney disease and leading cause of transplantation. A study presented on June 6th at ERA-EDTA 2021 revealed promising data in form of a Phase II study of iptacopan; an oral inhibitory approach to therapy for IgAN without the side effects of immunosuppression.

IgAN exists as the most common form of glomerulonephritis (GN), previously treated with immunosuppressive therapy; aiming to combat a complex inflammatory response causing progressive loss of kidney function. Evidence has categorised this method with increased incidence of adverse effects, especially infections, and led to criticism amongst experts. In this way, a niche exists for targeted therapy.

As a highly selective inhibitor, iptacopan can be applied to target chronic inflammation by blocking the alternative complement signalling pathway of the immune system. Investigations took form in a randomised double-blind placebo-controlled clinical trial, where 112 patients were evaluated in two stages. 46 IgAN patients were given three different doses iptacopan or placebo for 90 days, and then a further 66 four doses or placebo for 180 days; the endpoint being a dose-response relationship improving proteinuria.

All patient data was later evaluated combined, with secondary endpoints safety and tolerability, as well as estimated glomerular filtration rate and biomarkers of the alternative complement signalling pathway. Five groups of varying iptacopan dosage and placebo were compared, with four patients discontinuing treatment from side effects. Analysis presented a statistically significant dose-response effect against the placebo, a trend to stabilisation in renal function, and improved biomarkers. Side-effects were mild with no serious adverse effects, most commonly headache at 11.6%, with back-pain, diarrhoea, and vomiting all 6.3% and unrelated to dose taken.

Success of the trial is witnessed in progression to Phase III trials, Barratt who headed investigations summarised, "This is the first study to report the safety and efficacy of targeted alternative complement pathway inhibition in IgAN patients, with the results showing a significant dose-dependent reduction in proteinuria and a trend to eGFR stabilisation." ■

"Analysis presented a statistically significant dose-response effect against the placebo, a trend to stabilization in renal function, and improved biomarkers"

Understanding the Association between COVID-19 and Acute Kidney Injury

ACUTE kidney injury (AKI) in patients diagnosed with COVID-19 is on the rise, despite the fact that role of SARS-CoV-2 infection in the kidneys is not fully understood. At the early stages of COVID-19 pandemic, it was discovered that coronavirus caused a wide range of symptoms, along with the expected respiratory symptoms, diagnosed patients also had neurological, gastrointestinal, renal, and many more associated symptoms. These findings brought about the belief and understanding that COVID-19 virus may potentially be a multi-system disease and affects several organs directly.

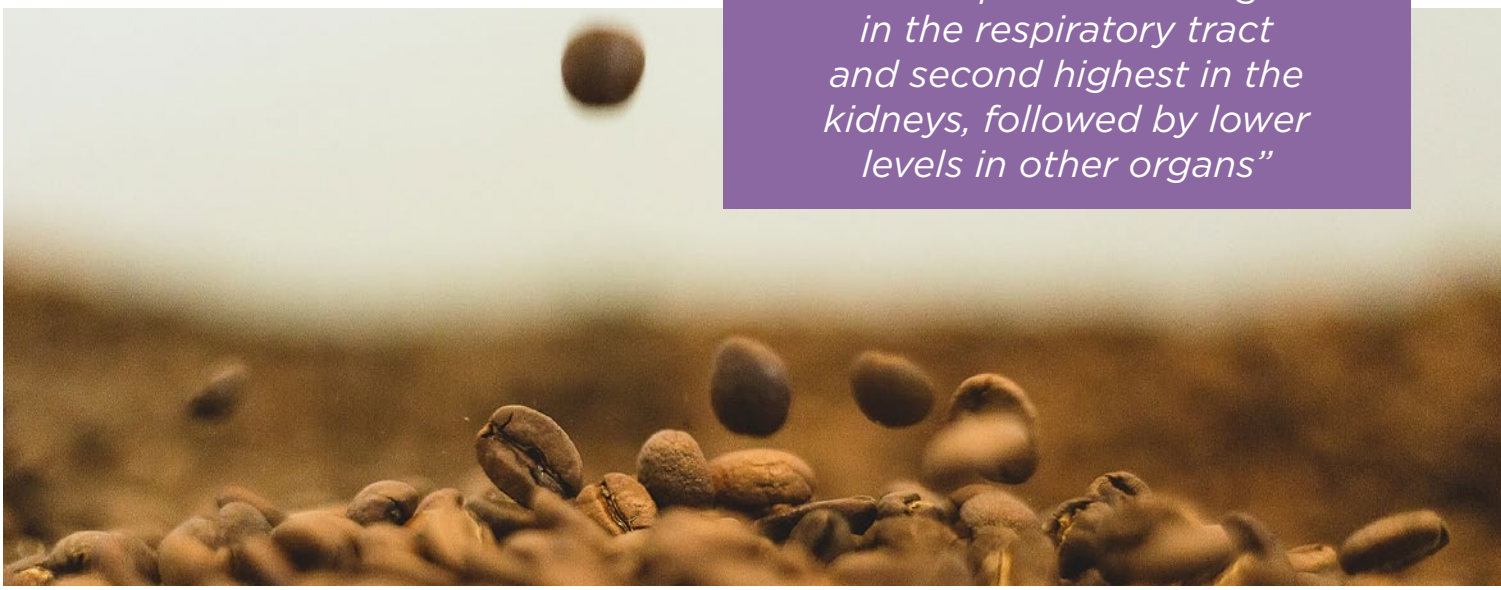
Authorities in Hamburg, Germany, in the spring of 2020, ordered autopsies to be executed on all the patients who had died from COVID-19. By this, they were able to collate the world's biggest autopsy database containing all organ systems. This post-mortem data collection was carried by forensic pathologists and has contributed to several organ-related COVID-19 primary research studies.

Tobias Huber, UKE Hamburg, Germany, discussed some of his research findings at opening ceremony of the ERA-EDTA Congress that took place on the 5th June 2021. COVID-19 patients have an elevated rate of AKI (56.9%) compared to other patients diagnosed with serious infections or sepsis (37.2%) in the intensive care unit. Additionally, 4.9% of COVID-19 diagnosed patients require a renal replacement therapy in comparison with 1.6% of patients diagnosed with other severe infections. A remarkable previous research led by Huber, showed that the COVID-19 virus load in a deceased patient was highest in the respiratory tract and second highest in the kidneys, followed by lower levels in other organs such as heart, liver, and brain.

An alternative autopsy study, with similar high comorbidity rate as in other studies, carried out by Huber and his team aimed to understand the correlation between renal tropism and outcome of COVID-19. Sixty-three autopsies were carried out and results showed that SARS-CoV-2 infection was identified directly, in 60% of the cases, in the kidneys. Furthermore, the results showed period of time between the diagnosis of COVID-19 and death was shorter when the virus was detected in the kidneys compared to absence virus in the kidneys, 14 days versus 21 respectively.

These studies and many more have associated COVID-19 with AKI, and identified it as multi-system disease, and have set a steppingstone potentially understanding why kidney injury is recurrent in patients diagnosed with COVID-19. ■

"the COVID-19 virus load in a deceased patient was highest in the respiratory tract and second highest in the kidneys, followed by lower levels in other organs"



"In patients with C3 glomerulopathy, targeted therapy aimed at the complement system provides the best possible route to slow disease progression"

Targeted Therapy Could Be Key to C3 Glomerulopathy Progression

ACCUMULATION of C3 protein in the glomeruli causes a rare immunological disease, C3 glomerulopathy (C3G). This deposition of the C3 protein causes severe inflammation of the glomeruli and renal dysfunction, progressing to final stage of kidney disease where diagnosed patients require dialysis and possibly a kidney transplant after 10 years. There is currently no approved treatment for C3G, however, a new study illustrated that blocking the inflammatory C5a receptor with avacopan, could be an effective method of slowing the progression of C3G.

The Controlled Trial Evaluating Avacopan in C3 Glomerulopathy (ACCOLADE) study was presented at the ERA-EDTA congress that took place in 5–8th June 2021. Currently C3G is treated by lowering of both blood pressure and proteinuria, and by use of non-specific immunosuppression. For the future purpose of comparing different therapeutic methodologies, a 'European Register for C3 glomerulopathy and immune-complex-mediated MPGN', in which cases are consistently recorded, was launched in 2015.

The ACCOLADE study conducted a randomised, double-blind, placebo-controlled analysis of the use of avacopan in patients diagnosed with C3G over a period of 26 weeks. The participants received either 30 mg of avacopan twice daily (n=28), or placebo (n=29), both administered orally. A C3G Histologic Index (C3HI 'Disease Activity Score') was utilised to calculate changes in histology throughout the study. The higher values of the C3G histologic index suggested severe disease progression. Remarkably, at 26 weeks, the C3HI activity score improved by 0.2% in the avacopan group but exacerbated by 20.6% in the placebo group. The C3HI chronicity score increased by 31.7% in the avacopan group and by 57.5% in the placebo, equating to a total change of 0.8 versus 1.6, respectively. Additionally, proteinuria result levels, also included in the ACCOLADE study, displayed notable improvement in the group of patients using avacopan.

Preclinical studies indicate that C3G disease progression is noticeably decelerated by avacopan, a selective C5a receptor inhibitor. "In patients with C3 glomerulopathy, targeted therapy aimed at the complement system provides the best possible route to slow disease progression," explained Bomback. "In addition, the more selectively we target the causal disease mechanisms in the immune system, as was done in this study at the C5a receptor with avacopan, the less the immune system as a whole is suppressed, which should also yield not only more effective but also less toxic therapies.' ■

Mechanisms of Kidney Protection by Gliflozins

GLIFLOZINS, or SGLT2 inhibitors, are oral anti-diabetic drugs that reduce blood sugar and improve cardiovascular and renal outcomes in patients with or without diabetes. A recent study has shown SGLT2 inhibitors slow the progression of chronic kidney disease (CKD) via correlations with the individual's haematocrit value regardless of their diabetes status. The results of this new study were presented as part of a press release at ERA-EDTA.

The EMPA-REG OUTCOME study by Christoph Wanner, University of Würzburg, Germany, showed the wider benefits of SGLT2 inhibitors extending beyond the known effects of lowering blood sugar and that the rate of cardiovascular events in patients with type 2 diabetes is significantly reduced if the SGLT2 inhibitor empagliflozin is administered.

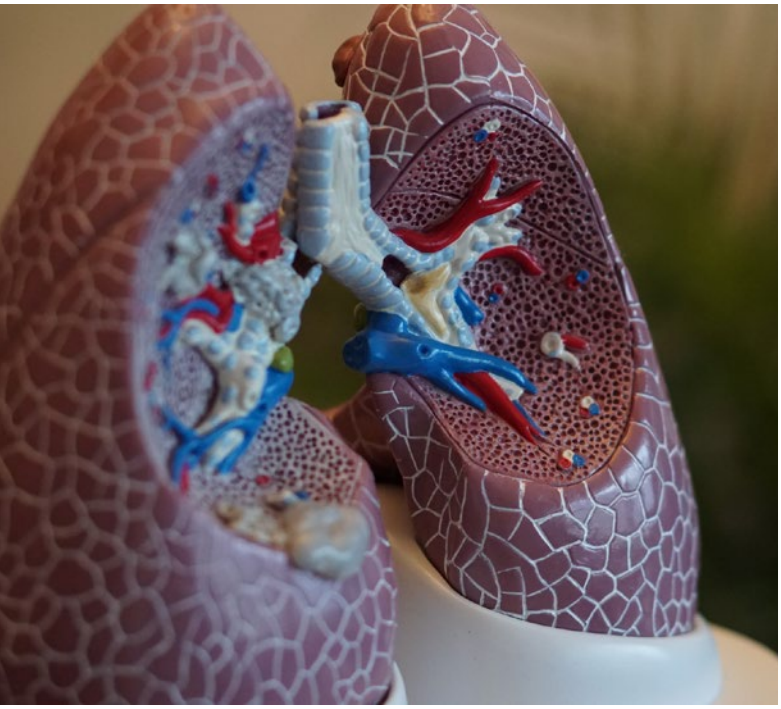
The mechanisms by which SGLT2 inhibitors produce their renoprotective effect are still largely unknown. The study group carried out a post-hoc analysis using data from the EMPA-REG OUTCOME study to identify potential factors that could mediate or be correlated with the renoprotective effects of SGLT2 inhibitors. The pooled treatment group (empagliflozin 10 and 25 mg/day) was compared with the placebo group. From different physiological areas, 17 different potential factors were registered at the start of the study and statistically evaluated on a time-dependent basis and at Week 12 for orientation point analysis. The variables were incrementally summed according to the strength of their effect on the composite renal endpoint.

In more advanced CKD stages, the kidneys no longer produce sufficient amounts of erythropoietin, and the patient may be diagnosed with renal anaemia measured by reduced haematocrit levels. After adjusting the haematocrit value over time, the study group found the haematocrit was the strongest mediator of renoprotective effects. Other factors included serum uric acid concentration, albuminuria, HbA1c, blood pressure, and fatty acid levels.

"According to the new study data, haematocrit is the most important mediator of the positive gliflozin effects, i.e., the main mechanism by which the SGLT2 inhibitors stabilise renal function and improve the clinical outcome correlates with the percentage increase in erythrocytes."

"We know that severe anaemia is a predictor not only for CKD progression, but also for cardiovascular events," explained Wanner. "According to the new study data, haematocrit is the most important mediator of the positive gliflozin effects, i.e., the main mechanism by which the SGLT2 inhibitors stabilise renal function and improve the clinical outcome correlates with the percentage increase in erythrocytes." ■

Lung Sonography Could Be Useful in Identifying Lung Decongestion in Patients Undergoing Haemodialysis



LUNG congestion, a condition whereby water accumulates within the lungs, is common in patients who are undergoing haemodialysis especially in those that have a high risk of developing cardiovascular disease such as coronary heart disease or heart failure. X-ray imaging is the current preferred method used to identify this congestion, compared to a stethoscope. Progression of the lung congestion severely impairs and compromises the pulmonary gas exchange leading to shortness of breath and, in some cases, death.

Patients undergoing haemodialysis have higher mortality rate correlating to lung congestion, as all the fluid presented during dialysis session is retained. However, the severity of overhydration and lung congestion can be analysed by sonography, a type of ultrasound imaging. An international, multicentre study assessing this ultrasound methodology was presented in the ERA-EDTA Congress on 6th June 2021. The study, involving 363 patients, used mortality, heart attack and decompensated heart failure as primary endpoints to assess the patient outcomes.

The study was divided in two groups, in the first group the ultrasound was carried out by unblinded nephrologists who knew that patients were going through dialysis treatments, whilst the control group was carried out by blinded cardiologists who had no knowledge of treatment. The parameters of measurement within the study were B-lines in the ultrasound image which displayed fluid accumulation within the lung tissue. Haemodialysis management target required was less than 15 B-lines.

The results of the study showed that the number of B-lines reduced from 15 to nine from the start to the end of the study sonography group (n=183). However, in the control group (n=180) the number substantially increased from 16–30. Additionally, 117 patients in the sonograph group (78%) reached the target value (<15 B-lines). "The lung ultrasound-guided treatment strategy significantly reduced individual secondary, post hoc endpoints: decompensations of heart failure occurred 63% less frequently and severe cardiovascular events 37% less frequently," concluded Claudio Torino, Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension of Reggio Calabria, National Council of Research, Institute of Clinical Physiology, Reggio Calabria, Italy. ■

"Patients undergoing haemodialysis have higher mortality rate correlating to lung congestion, as all the fluid presented during dialysis session is retained. However, the severity of overhydration and lung congestion can be analysed by an ultrasound imaging, sonography"

Dapagliflozin Provides Protection Against Focal Segmental Glomerulosclerosis

EMPLOYING dapagliflozin treatment has provided favourable renal outcomes in patients of chronic kidney disease (CKD). This SGLT-2 (sodium dependent glucose co-transporter) inhibitor was assessed through the DAPA-CKD study, and the significant benefits to patients with FSGC (focal segmental glomerulosclerosis) discussed on 6th June ERA-EDTA 2021.

In a treatment path frequently resulting in dialysis, demand exists for a new approach to stabilise and protect kidney function; this SGLT-2 inhibitor was investigated as an alternative to glucocorticoids and supportive therapy, with study led by David Wheeler, Professor at University College London. Findings concluded that dapagliflozin markedly reduces risk of progressive loss in renal function for patients of CKD, both in the presence and absence of diabetes mellitus.

"Findings concluded that dapagliflozin markedly reduces risk of progressive loss in renal function for patients of CKD, both in the presence and absence of diabetes mellitus."

Success of the inhibitor stems from its action in the proximal renal tubule, to increase urinary glucose excretion. This was analysed among 115 participants with FSGS, randomised to receive 10 mg or placebo on top of standard treatment. The combined primary endpoint included a 50% decrease in glomerular filtration rate (eGFR), dialysis requirement or cardiovascular death.

Tolerability and safety profiles for dapagliflozin were good, with similar discontinuations in both groups. 4 (7.5%) of the treated patients and 9 (14.5%) on placebo reached the primary endpoint, with comparative annual eGFR loss -1.9ml/min/1.73m^2 in the dapagliflozin versus -4.2 ml/min/1.73m^2.

Results from similar studies present SGLT-2 inhibitors helpful at improving cardiovascular and kidney outcomes with patients of type 2 diabetes, but this study extends findings to patients who do not have diabetes. This was explained at ERA-EDTA by Wheeler, "SGLT2 inhibitors offer a promising new therapeutic option in the field of nephrology and are likely to be used more extensively in future, both in diabetic and non-diabetic kidney diseases. Not only do these agents slow progression of kidney disease, but they also reduce the risk of cardiovascular diseases, which are important comorbidities in this patient population."

Critics will acknowledge the study size and demographic, such as average age 53±13.9 years, and warrant widening the sample to carry the promising results with greater scientific weight. ■

Innovations in Haemodialysis

Evan Kimber
Editorial Assistant

Citation: EMJ Nephrol. 2021;9[1]:24-26.

THE 'INNOVATIONS in Haemodialysis' session of this year's European Renal Association –European Dialysis and Transplant Association (ERA-EDTA) Virtual Congress 2021 focused on discussing important inclusions to the design and development of new haemodialysis (HD) therapies. Presentations elaborated upon the expected direction for portable dialysis machines, the progressions in expanded HD (HDx) using new membranes, and strategies to reduce organ ischaemia with modern technology.

Karin Gerritsen from the Utrecht University Medical Centre, the Netherlands, opened the session by contextualising the transition of dialysis machines and their expected course of progression. Marie Evans from the Karolinska Institutet, Solna, Sweden, complimented these insights by describing new advancements in HDx, and Christopher McIntyre from the University of Western Ontario, Canada, described some of the modern initiatives that aim to reduce the existing issues associated with HD.

THE JOURNEY TOWARDS PORTABLE DIALYSIS

A commonly emerging theme in this session was the slow rate of advancement in the concepts and practice of HD since its conception; Gerritsen begun by recognising Willem Kolff as the father of HD and described the bulky, impractical devices in use today as not too dissimilar to those of his invention. Currently, there are several compact HD machines on the market that use low dialysate volumes for short, daily dialysis, but Gerritsen emphasised a key goal in modern nephrology is to provide an implantable kidney. Describing the latest developments in the field, she outlined several portable devices under development that do not require a fixed water supply.

Current challenges in miniaturisation include difficulty removing urea from dialysate, achieving high clearance with a low dialysate volume or flow, plus ensuring toxic uraemic clearance. However, Gerritsen highlighted that strategies involving electro-oxidation and biohybrid systems are under investigation to combat these problems.

NEW DEVICES AND THEIR FUTURE EXPECTATIONS

Developing an implanted kidney is a concept of the future, considering that most devices today are single-pass HD machines and weigh 20–35 kg. Gerritsen mentioned how emerging miniature dialysis devices are showing promise through employing regeneration of dialysate, ahead of a water supply. For example, NextKidney and Wearable Artificial Kidney devices incorporate a purification unit, which creates a closed loop, improving the practicality of a wearable machine. These continuous-flow peritoneal dialysis devices use recirculation

dialysis technology once per day to effectively remove urea and maintain more stable glucose concentrations; they are expected to become available soon and future innovations could facilitate the steps in miniaturisation to wearable dimensions.

EVIDENCE OF IMPROVEMENTS WITH NEW MEMBRANES?

Evans gave insight on middle molecule (MM) accumulation associated with dialysis-related issues, such as anaemia. Difficulty lies with clearing molecules larger than 50 kDA; with standard diffusive transport in dialysis, convective clearance remains dependent on ultrafiltration rate and sieving coefficient. Evans highlighted that there is greater clearance of MM with large convective volumes during haemodiafiltration (HDF) and referenced two large randomised controlled trials comparing high-flux HD with HDF.

She then discussed several long-term studies investigating medium cut-off membrane (MCO) dialysis; compelling evidence describes safe and effective treatment whereby increased pore size is shown to improve clearance rate. Consequently, MCO dialysers improved quality of life, specifically by reducing the symptoms of pruritis, restless legs, and recovery time. It should be noted, however, that this technique poses a risk in exposure to endotoxins and is limited by its failure to improve clinical outcomes such as mortality, hospitalisation rates, and cardiovascular events.

HAEMODIALYSIS THERAPY TODAY

According to Evans, HDx could offer a cost-effective alternative in patients without access to HDF who do not achieve substitution volumes of 23 L, based on improvements in MM clearance outlined at normal blood flows. Demand for water, a limited resource, is also less than in HDF, making HDx a more environmentally friendly option for symptomatic improvement. Evans highlighted the possibility that MCO membranes might be able to offer treatment at home with standard dialysis fluid in the near future.

ORGAN ISCHAEMIA DURING HAEMODIALYSIS

Last in proceedings, McIntyre begun by referencing a similar talk he delivered at ERA–EDTA 2004 and emphasised that he felt there has been little change since then. He raised a two-fold problem concerning the specialists and industrial partners involved in HD: not caring enough about the topic; embedded in a conservative, poorly funded, and un-innovative market in dire need of refreshment.

"...future innovations could facilitate the steps in miniaturisation to wearable dimensions."

"Demand for water, a limited resource, is also less than in HDF, making HDx a more environmentally friendly option for symptomatic improvement."

McIntyre expanded on a need for change, highlighting the strong existing evidence that current HD practice results in multiple, segmental ischaemic insults that are cumulative and result in fixed injury. This is particularly detrimental in cardiac tissue and the brain, where cytotoxic oedema appears during dialysis and is harmful to white matter, reducing cognitive performance.

CAN MODERN TECHNOLOGIES HELP?

McIntyre outlined the opportunities for biohacking, involving permanent implants that offer a sensitive vasomotor control for dialysis, alongside monitoring devices to personalise treatment based on markers such as ultrafiltration rate and cardiovascular stress. He described the dangers of sodium storage, a crucial uraemic toxin: microscopy has demonstrated impaired function of the endothelial proteoglycan layer, which facilitates sodium transport, and accumulating high levels is associated with reduced survival in patients receiving renal replacement therapy.

Moving on, McIntyre briefly described the studies underway analysing peritoneum implants, subcutaneous pumps, and bladder catheters as examples of research aimed at improving dialysers through the use of emerging magnet initiatives. He finished by running through a mathematically modelled simulation of myocardial perfusion with electrophysiological activity as an example of the individualised dialysis under development, and stressed the importance of funding research partners.

FUTURE DIRECTIONS

Reflecting on the barriers to progression in his concluding remarks, McIntyre commented: "I'm not hopeful for the next 2-3 years, but beyond that these solutions could work for various stakeholders." He went on to suggest that "society has a reason to take note of dialysis: they don't currently realise how much they are paying for it." ■

Future Scenarios for Renal Disease Associated with Climate Change

Janet Nzisa

Editorial Assistant

Citation: EMJ Nephrol. 2021;9[1]:27-29.

CLIMATE CHANGE AND NEPHROLOGY: COULD CLIMATE CHANGE AND HEAT STRESS CAUSE CHRONIC KIDNEY DISEASE?

ONE of the highlights of this year's European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) congress, was the session on future scenarios for renal disease. The session opened with a presentation by Richard Johnson, University of Colorado, USA, who discussed how climate change can impact nephrology.

Undoubtedly, climate change and its impact on the environment has been an ongoing topic of interest for researchers for some time. Johnson started the session by explaining that the mean temperatures have increased by 0.8°C since 1880, with two-thirds of this rise occurring between 1975 and 2021. With climate change being the root cause of 75% of heatwaves and, given the consequences that heatwaves have on population health, it comes as no surprise that climate change would be a point of interest for healthcare professionals. In fact, global warming has brought about severe heat waves, which have been linked to heat strokes and cardiovascular events. Johnson highlighted that heat strokes could have serious complications including seizures, multi-organ failure, and, in extreme cases, death.

Common kidney manifestations of heat stroke include volume depletion and hypotension. During a severe heatwave, an individual can sweat up to 10–12 L/day, which can lead to electrolyte abnormalities such as hyper- or hyponatraemia and hyper- or hypokalaemia. Other kidney manifestations include acute kidney injury, especially acute interstitial nephritis, and rhabdomyolysis. Johnson also explained that patients with kidney failure after a heat stroke are at higher risk of developing a chronic kidney disease (CKD) and end-stage renal disease.

Johnson put forward the argument that there was a direct geographical correlation between increase in temperature over the last 50 years and the location of epidemics of CKD. He presented data showing that CKD death rates correlate with rising temperatures, especially in hot regions such as Central America, India, Thailand, and Sudan, where people are more likely to be employed in manual labour.

In another recent study, a rise was observed in the mortality rates of 120,000 Nepali manual workers who migrated to Qatar. The results of this study showed a cardiovascular mortality rate of 1,500 million/year caused by heat stroke, with most of these individuals also diagnosed with CKD. A study from Taiwan carried out over 13 years showed a 4-fold increased risk for developing CKD and 9-fold increased risk for end-stage renal disease in patients who experienced a heat stroke. Another study carried out in Taiwan over a period of 14 years further revealed that any associated heat events, such as heat exhaustion, heat fatigue, heat cramps, and heat syncope, may potentially increase the risk of developing kidney disease in the future.

CKD epidemics occur in the hotter regions of the world where the majority of the population does manual work. The Uddanam nephropathy epidemic in India lasted from 1961 to 2010 and occurred mainly in areas that experienced frequent heatwaves. Further to this, a study based on death records revealed a positive correlation between the CKD epidemic and rising temperatures. The study showed an association between mortality rates and CKD in Guanacaste on the Pacific coast of Costa Rica, which is a region with temperatures that have continuously increased since the 1970s. This increase could be attributed to the type of work of the individuals carried out. For example, manual labour involves heavy physical work, which may lead to severe distress in the body, especially working in high temperatures and humidity where conditions may exceed the recommended standards of the Occupation Safety Health Administration (OSHA).

Another study comparing the serum creatinine levels between individuals working in sugarcane fields in hot coastal regions and populations living in cooler high altitude regions showed the former had a higher chance of developing CKD. The increase in uric acid production and creatinine over time deteriorates renal functions.

Interestingly, there are similarities in presentations of CKD and heat stroke such as fever, leukocytosis, elevated C-reactive protein caused by inflammation, and renal manifestations such as acute kidney injury, absence of rhabdomyolysis, and the presence of sterile pyuria. A controlled study carried out on mice cells by Johnson and his team further delineated how CKD can be caused by repetitive heat and dehydration cycles. An alternative study on Mesoamerican nephropathy indicated that hydration and shade could provide renal protection. The results showed that by drinking up to 10 L of water with 2 L electrolytes a day, the levels of serum creatinine were lower and therefore preserved renal function overtime.

In his closing remarks, Johnson summarised that the pathology of kidney injury associated with heat stroke is mainly due to severe sweating, dehydration, and electrolyte abnormalities.

Appropriate hydration with electrolytes could partially reduce heat stress and the risk of damage to the kidneys caused by a heat stroke. However, climate change and global warming may further heighten the current ongoing CKD epidemics and mortality rates in hot regions.

PLANETARY HEALTH AND LIFESTYLE DISEASES

The environmental crisis caused by climate change is challenging humanity to an unprecedented degree. Traditionally, medicine is based on the understanding of the systems within the human body. In current times medicine needs to broaden its scope to start addressing the external environmental systems that have an influence on overall human health and the population. Innovative solutions are required in order to tackle this global crisis.

In a presentation on planetary health and lifestyle diseases, Peter Stenvinkel, Karolinska Institute Stockholm, Sweden, remarked: "We as nephrologists must know that the health of our patients is very much dependent on the environment, the welfare of animals, and other species in the environment." He continued by stating that the burden of lifestyle diseases increases and accumulates throughout the ageing process. These lifestyle diseases include cancer, heart conditions, Alzheimer's, depression, obesity, diabetes, liver, and kidney-related diseases, and have been associated with chronic inflammation, which Stenvinkel termed as the process of 'inflammageing'.

Stenvinkel explained that during stressful situations and experiences, the human body upregulates Nrf2, which in turn upregulates hundreds of anti-inflammatory and anti-oxidative genes. Stenvinkel introduced a study on the integrative biology and transcription networks that are involved in CKD, which showed that the Nrf2-mediated oxidative stress response pathway serves as a hub between the clusters of inflammation and metabolism-related pathways. Further research has shown the involvement of Nrf2 pathways in lifestyle diseases; in fact, Nrf2 depletion, mitochondrial dysfunction, loss of gut biodiversity, and oxidative stress all lead to overall 'inflammageing', thus contributing to the development of lifestyle diseases.

Among several interesting points discussed by Stenvinkel was gut biodiversity, something that could, in fact, be affected by the warming climate as shown by a study. Interestingly, there is now a hypothesis that loss of biodiversity on earth could actually affect gut biodiversity. As a rapidly changing ecosystem, the gut and the effect of environmental factors could have a huge impact on human health. At a nephrology level, a lack of biodiversity in gut microbiota in patients diagnosed with CKD undergoing haemodialysis has a negative effect on the outcome of the treatment.

Stenvinkel also discussed the concept of using food as medicine through the 'foodome', a new discipline that studies the food and nutrition domains through the application and integration of advanced omics technologies, using a personalised approach to nutrition and consumption of specific foods to target diseases.

Concluding his presentation, Stenvinkel explained that by reducing food waste and following a plant-based diet, more than two-thirds of biodiversity loss could be avoided. He also stated: "There will be no protection from overall pandemics unless we fix the planet food systems." This is undoubtedly a key message not only for nephrologists and healthcare professionals, but also for the general public. Stenvinkel explained how important it is to develop an arena for different disciplines to work together in finding a solution.

Secondary Hyperparathyroidism in Non-dialysis Chronic Kidney Disease

This presentation was part of a symposium that took place on 6th June 2021, as part of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) 58th Congress (Virtual)

Speakers: Michael Germain[1,2]

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Meeting Summary

Secondary hyperparathyroidism (SHPT) can manifest early in chronic kidney disease (CKD) and is associated with significant morbidity and mortality. As such, it is a key feature of CKD that should be assessed and treated from early in the disease. Parathyroid hormone (PTH) levels, greatly increased above reference ranges in SHPT, are controlled via vitamin D receptors; hence, there is an intimate relationship between levels of vitamin D and PTH, as the former suppresses the latter. Clinical studies show that people with CKD may require higher serum 25-hydroxyvitamin D (25[OH]D; calcifediol) target levels than those without CKD to compensate for decreased kidney activation of 25(OH)D to 1,25-dihydroxyvitamin D (1,25$[OH]_2$D; calcitriol). While SHPT can be managed by addressing vitamin D insufficiency, current approaches have limitations in that they either do not reliably and consistently lower PTH levels, as shown with cholecalciferol and ergocalciferol, or they can increase hypercalcaemia risk, as shown with active vitamin D/analogues. Extended-release calcifediol can control SHPT by steadily increasing 25(OH)D levels over time, leading to sustained lower PTH levels with minimal increases in levels of calcium or phosphorus.

Introduction

Chronic kidney disease can result in morbidity and mortality not only due to renal dysfunction itself, but also to associated conditions.[1] Declining kidney function can result in poor phosphate excretion, with subsequent increases in serum phosphorus and the bone-derived phosphaturic hormone fibroblast growth factor (FGF-23), along with reduction in vitamin D activation from 25(OH)D (calcifediol) to 1,25$(OH)_2$D (calcitriol).[2]

Consequences of such renal dysfunction include disruption in bone mineral metabolism, which can lead to vascular calcification and subsequent cardiovascular disease; bone abnormalities, which can increase fracture risk; and parathyroid gland hyperplasia, due to increased parathyroid hormone synthesis and release, known as

SHPT.[2,3] As such, recognition and treatment of CKD mineral and bone disorder (CKD-MBD) parameters are vital to avoid these potentially life-altering, and sometimes fatal, complications.

Here the author provides an overview of a presentation by Michael Germain, focusing on SHPT. Germain is a transplant nephrologist at Bay State Medical Centre in Springfield, Massachusetts, USA, and a Professor of Medicine at Tufts University School of Medicine in Boston, Massachusetts, USA. This symposium was delivered as part of the ERA-EDTA 58th Congress (Virtual), 5th–8th June 2021.

Vitamin D Catabolism and Deficiency

Vitamin D, from ultraviolet B radiation (as vitamin D3, cholecalciferol) or dietary sources (as vitamin D2, ergocalciferol; or D2), is converted first in the liver to 25(OH)D then in the kidney, parathyroid gland, or other extrarenal tissue such as macrophages, endothelial cells, and the colon, to the active form $1,25(OH)_2D$.[4] This latter conversion, catalysed by the enzyme 1-α-hydroxylase, can be regulated by PTH and FGF-23.[4-6] Both of these forms of vitamin D can be catabolised by 24-hydroxylase to inactive forms, respectively $24,25(OH)_2D$ and $1,24,25(OH)_3D$.

Deficiency in vitamin D is generally defined as serum 25(OH)D levels <20 ng/mL, with insufficiency being 20–29 ng/mL.[7] Germain explained how in North-Eastern USA, and presumably other countries in northern latitudes, there is a high incidence of 25(OH)D insufficiency in the general population. This is exemplified by the USA's National Health and Nutrition Examination Survey (NHANES) III 2001–2004 data that revealed very low levels of 25(OH)D (<12 ng/mL) in 3.7% of the general population, with 22.2% showing levels <20 ng/mL.[8]

In patients with CKD there is increased 25(OH)D and $1,25(OH)_2D$ catabolism and decreased $1,25(OH)_2D$ production because of increased FGF-23.[3-9] This exacerbates the effective deficiency of $1,25(OH)_2D$ compared to healthy individuals, leading to a high prevalence in this population of low serum 25(OH)D and $1,25(OH)_2D$.[4,5,9-11] Such deficiencies have been observed in a study of people with CKD where 57% and 14% of patients at Stage 3 (n=65) had low (10–30 ng/mL) or very low (<10 ng/mL) levels of serum 25(OH)D, respectively, with percentages for Stage 4 patients (n=113) being 58% and 26%, respectively.[12] In the CKD Stage 5 dialysis population, vitamin D deficiency aggravates to 47% (low) and 42% (very low).[13] As patients with CKD with lower 25(OH)D levels have been shown to have higher plasma PTH; this translates to a potential need for patients with CKD to require higher serum 25(OH)D target levels than a healthy population.[5,14-16]

Secondary Hyperparathyroidism Development

"SHPT is a very long disease," reported Germain. "It starts very, very early in CKD, before we even see [a patient] and…it progressively goes up."

PTH and vitamin D have an intimate relationship whereby PTH stimulates $1,25(OH)_2D$ synthesis, which negatively feeds back to the parathyroid glands to decrease PTH synthesis and release via vitamin D receptors.[2] As such, while sufficient levels of $1,25(OH)_2D$ mean PTH suppression, decreased $1,25(OH)_2D$ levels can lead to an increase in PTH release and so to the development of SHPT.[2,17] Other factors, such as low serum calcium, increased serum FGF-23, and high serum phosphorus, can also lead to increased PTH synthesis and secretion with diagnosis of SHPT (Figure 1).[2,11]

As highlighted by Germain, SHPT can start early in CKD and become progressively worse with renal decline.[2] For instance, a study[11] involving 1,814 patients from 153 centres in the USA showed elevated intact PTH (iPTH; >65 pg/mL), denoting SHPT, in approximately 12% of patients with an estimated glomerular filtration rate (eGFR) of 80 mL/min/1.73m^2 (Stage 2), with steady increases occurring as CKD progressed so that by late Stage 4/Stage 5 (eGFR <20 mL/min/1.73m^2), almost 90% had elevated iPTH.[11] Germain noted that in this study, as in his practice, abnormal calcium (<8.4 mg/dL) and phosphorus (>4.6 mg/dL) levels were rarely observed in patients with Stage 2/3 CKD, but these became more prevalent in Stages 4 and 5, to approximately 20% and 40% of patients, respectively.[11]

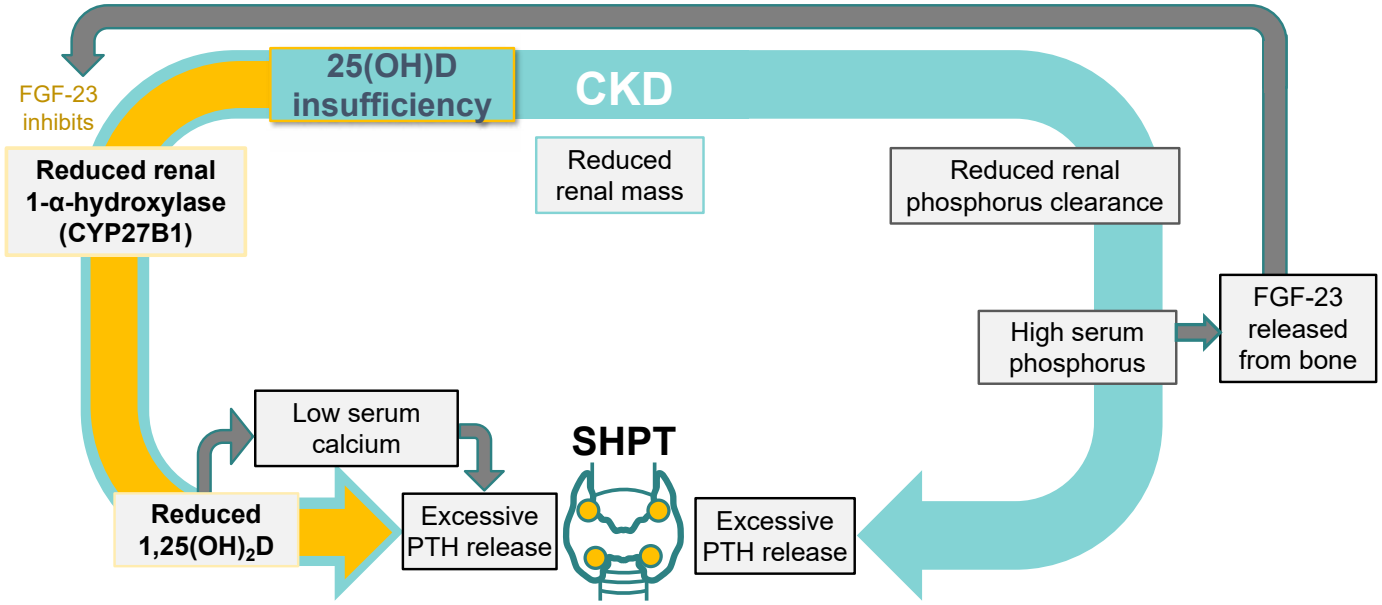


Figure 1: The relationship between low 25-hydroxyvitamin D levels and secondary hyperparathyroidism.[2,11]

CKD: chronic kidney disease; FGF-23: fibroblast growth factor 23; PTH: parathyroid hormone; SHPT: secondary hyperparathyroidism; $1,25(OH)_2D$: 1,25-dihydroxyvitamin D; 25(OH)D: 25-hydroxyvitamin D.

Consequences of Secondary Hyperparathyroidism

Germain highlighted that SHPT is important to recognise and treat early as it is associated with poor outcomes and becomes increasingly difficult to control. For patients on dialysis, SHPT can lead to parathyroid gland unresponsiveness to treatments such as activated vitamin D and calcimimetics, resulting in the need for a parathyroidectomy and subsequent need for control of hypoparathyroidism and potential surgical complications. His patient (Case Study) also demonstrated progressively rising PTH levels, which fits in terms of his association with rising risk for associated mortality, vascular events, and fractures.[19]

These poor outcomes are illustrated by an observational study that included 5,108 patients with Stages 3–4 CKD, showing that a steady increase in PTH levels was associated with an increase in the 10-year probability of fractures, vascular events, and death.[19] In another study,[20] involving 2,728 patients with CKD, elevated PTH prior to dialysis was strongly associated with uncontrolled SHPT during dialysis. Regardless of the use of active vitamin D or calcimimetics at this stage, patients who initiated haemodialysis with PTH >600 pg/mL had a 19% higher risk of untreatable SHPT compared to patients with 150–300 pg/mL levels of PTH.[20]

Germain highlighted some of the consequences of SHPT that he sees in his patients. Active bone disease, which increases the risk of fractures, can be seen in the fingers, with clear radial side and finger tuft bone resorption (Figure 2A). Increased vascular calcifications, shown in the abdominal vessels (Figure 2B), is, discussed Germain, associated with a risk for cardiovascular disease and peripheral vascular disease, as well as potentially preventing a patient from being able to undergo a kidney transplant due to calcified vessels not being amenable to anastomosis onto a transplanted kidney.

Case study presented by Germain.

A 58-year-old male weighing 120 kg, 170 cm tall. Has diabetes mellitus with presumed nephropathy and arterial hypertension; had a coronary artery bypass graft in 2018.

Patient was first seen by Germain in 2010, when, with CKD Stage 3a, his calcium and phosphorus levels were normal but his PTH levels were increased.

By 2017, both CKD stage and PTH levels had increased, and his vitamin D levels were low (vitamin D deficiency is generally accepted to be <20 ng/mL[2]).

	2010	2015	2017	2018*	2021*
PTH pg/mL	90	150	194	200	157
eGFR mL/min/1.73m^2	40.6	27.3	25.0	20.0	9.0
CKD stage	3a	4	4	4	5
Calcium mg/dL	n.d.	n.d.	8.9	8.7	8.9
Phosphorus mg/dL	n.d.	n.d.	3.6	4.3	7.8
Urine protein g/day	n.d.	n.d.	3.0	n.d.	n.d.
Vitamin D ng/mL	n.d.	n.d.	14.6	23.9	70.9

First treatment goal would not be to normalise PTH but, according to Germain: "to prevent it from progressing to the point of where it will become untreatable as the patient approaches/goes on to dialysis."

• PTH should be measured every 3 months for more advanced CKD stages.

4,000 IU cholecalciferol daily was prescribed in 2017.

• 25(OH)D levels remained low (14.6 ng/mL), potentially, discussed Germain, due to the nephrotic range proteinuria (3.0 g/day) leading to decreased protein available for 25(OH)D transport and because of increased 25(OH)D catabolism.

PTH levels continued to increase (2017).

• Patient was then treated with a fairly low dose of calcitriol (1.0 µg three times per week) but became hypercalcaemic (not shown in table).

• KDIGO guidelines state: "In adult patients with CKD G3a–G5 not on dialysis, do not routinely use calcitriol and vitamin D analogues (2C). It is reasonable to reserve the use of calcitriol and vitamin D analogues for patients with CKD G4–G5 with severe and progressive hyperparathyroidism (Not Graded)."[6]

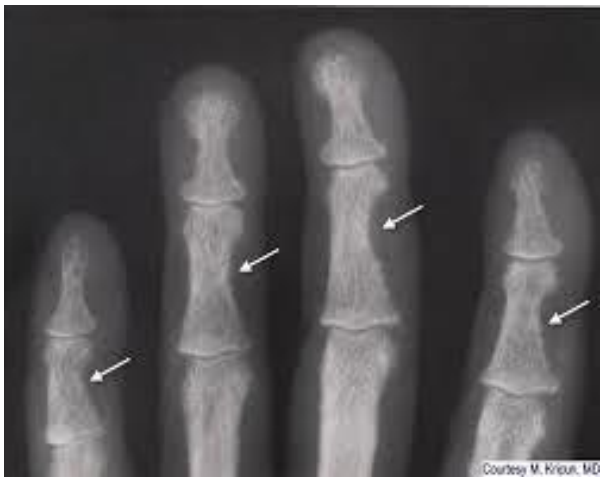
Germain initiated extended-release calcifediol in 2018.

• After 3 years, a decrease in PTH was maintained, with an increase in 25(OH)D and no change in serum calcium levels.

• Phosphorus increased as the patient approached end-stage renal disease, as is commonly seen; this was not expected to be due to extended-release calcifediol, as impact on phosphorus was limited in clinical trials.[18]

* ERC 30 µg initiated 2018.

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ERC: extended-release calcifediol; n.d.: no data; PTH: parathyroid hormone.



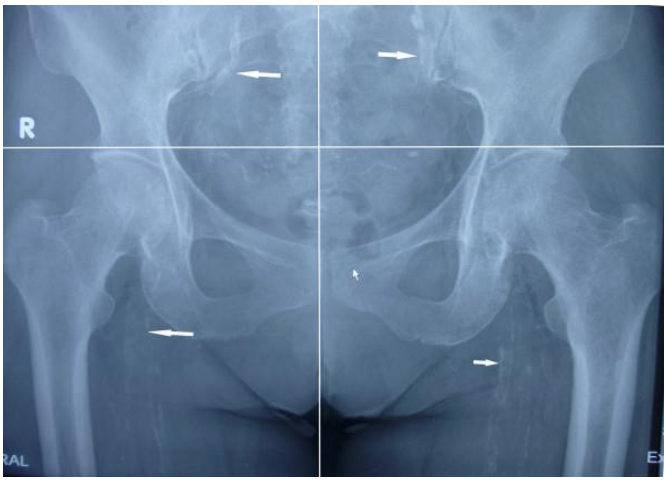


Figure 2: Consequences of secondary hyperparathyroidism.

A) Subperiosteal bone resorption in fingers. **B)** Vascular calcification of the hip and pelvis.

Treatment for Secondary Hyperparathyroidism

As optimal PTH levels in people with CKD are not known, the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for non-dialysis patients with CKD (Stages 3a–5) recommend that in patients where levels of iPTH are progressively rising or are persistently above the upper normal limit, evaluation should be made of modifiable factors, including hyperphosphataemia, hypocalcaemia, high phosphate intake, and vitamin D deficiency.[6] They suggest that for those on dialysis, the iPTH range should be maintained between 2–9 times the upper limit of the normal range.[6]

An ideal treatment for SHPT would increase 25(OH)D levels to physiologic ranges only, decrease PTH levels, and have no impact on levels of calcium, phosphorus, and FGF-23 (Table 1).[21]

In people with CKD (non-dialysis or dialysis), 25(OH)D supplementation with cholecalciferol or ergocalciferol is the initial recommendation for 25(OH)D deficiency, with vitamin D prohormone, as immediate-release (IR) calcifediol, also considered.[6,21,22] However, these treatments only moderately increase 25(OH)D levels and have a non-reliable and non-consistent effect on PTH, with IR calcifediol slightly increasing levels of FGF-23, which can lead to breakdown of 25(OH)D and $1,25(OH)_2D_3$ and reduced generation of $1,25(OH)_2D_3$ (Table 1).[21,27,28]

Active vitamin D ($1,25[OH]_2D_3$) or vitamin D analogues, such as alfacalcidol, calcitriol, or paricalcitol, may be considered next for both non-dialysis and dialysis patients (Table 1).[21,24-26] However, while vitamin D analogues can suppress PTH more strongly, they can also result in a large rise in calcium, phosphorus, and FGF-23 levels, all without a substantial beneficial effect on serum 25(OH)D.[21,29]

Extended-Release Calcifediol

A study in rats showed that administration of IR calcifediol led to high serum levels of both 25(OH)D, with an immediate spike following injection, and $1,25(OH)_2D$, with a spike a few hours later.[23] Of note, levels of 25(OH)D remained very high for at least 25 hours post-injection and, notably, the amount of detectable $1,25(OH)_2D$ dropped to near-baseline levels by 25 hours.

These findings in an animal study fit into the postulate that pharmacological surges of serum 25(OH)D may trigger negative feedback of endogenous vitamin D signalling, inducing catabolism.[5] Indeed, this was shown in a clinical study where the same 25(OH)D initial spike seen in rats was shown in participants who received a 448 mg bolus of IR calcifediol, with levels remaining high for at least 4 days.

Table 1: Effect of current treatment options on secondary hyperparathyroidism parameters in non-dialysis/dialysis patients with chronic kidney disease.[21,22,23-26]

Drug	Active	25(OH)D	Calcium	Phosphorus	PTH	FGF-23
Ideal SHPT treatment		↑	–	–	↓	–
Nutritional vitamin D	Cholecalciferol Ergocalciferol	↑	–	–	– ↓	–
Prohormone	IR calcifediol	↑	–	–	– ↓	↑
Active vitamin D/ analogues	Alfacalcidol Calcitriol Paricalcitol	↓	↑	↑	↓	↑

FGF-23: fibroblast growth factor 23; IR: immediate-release; PTH: parathyroid hormone; SHPT: secondary hyperparathyroidism; 25(OH)D: 25-hydroxyvitamin D.

Of interest, 25(OH)D catabolism, as illustrated by 24,25$(OH)_2$D levels in this study, increased over a period of 12 days then remained high (around 40 ng/mL) until at least Day 40 post-injection. This was postulated to be due to the 25(OH)D spike from IR calcifediol increasing levels of the hormone responsible for 25(OH)D breakdown, 24-hydroxylase, and of FGF-23 (Figure 1), as found in the rat study.[23]

A more recent development for SHPT treatment is extended-release (over 12 hours) calcifediol (ERC; European Union [EU] term: prolonged release calcifediol).[21,23] In contrast to the IR formulation, in the animal experiment, while administration of ERC still led to some increases of 25(OH)D levels at 5 hours post-dose, this was to within physiologic levels, which gradually fell over the next 20 hours. There was also a much gentler rise in 1,25$(OH)_2$D, that, unlike with IR calcifediol, led to increasing levels of this active form of vitamin D over time (up to 25 hours post-dose). These were far lower levels than with the IR formulation and kept within the physiologic range. In the human study, a single dose of extended-release calcifediol (450 or 900 mg) did not lead to a spike in 25(OH)D but achieved a steady-state level over 4 days. There was decreased 25(OH)D catabolism, shown by significantly lower 24,25$(OH)_2$D levels compared to IR calcifediol over the 40 days post-administration.[23] This, suggested Germain, meant that extended-release calcifediol could "normalise the homeostatic response to vitamin D by PTH."

To examine the impact of ERC on not only 25(OH)D but also PTH, calcium, and phosphorus levels, two Phase III clinical trials (Study A and Study B) of ERC were carried out, including a total of 429 adults with non-dialysis CKD Stage 3–4, SHPT (iPTH: 85–499 pg/mL), vitamin D insufficiency (25[OH]D: 10–29 ng/mL), calcium levels 8.4–9.7 mg/dL, and phosphorus levels 2.0–4.9 mg/dL.[18]

Participants were stratified by CKD stage and received either 30 µg ERC daily or placebo for 12 weeks in a 2:1 ratio. For the following 14 weeks, the ERC group either remained on 30 µg ERC daily or the dose was increased to 60 µg if PTH >70 pg/mL, 25(OH)D ≤65 ng/mL, and serum calcium <9.8 mg/dL. In an open-label extension, the placebo group was switched to 30 µg ERC daily for 12 weeks, with those taking ERC remaining on the same dose. After 12 weeks, any participant with PTH >70 pg/mL and serum calcium <9.8 mg/dL were switched to 60 µg ERC daily for 14 weeks.[18]

The primary endpoint to this study, a ≥30% decrease in iPTH from baseline, was met by both studies (Figure 3A), with 33% and 34% of patients in Studies A and B, respectively, achieving this at Week 26 with ERC, compared with 8% and 7% of placebo patients, respectively.[18]

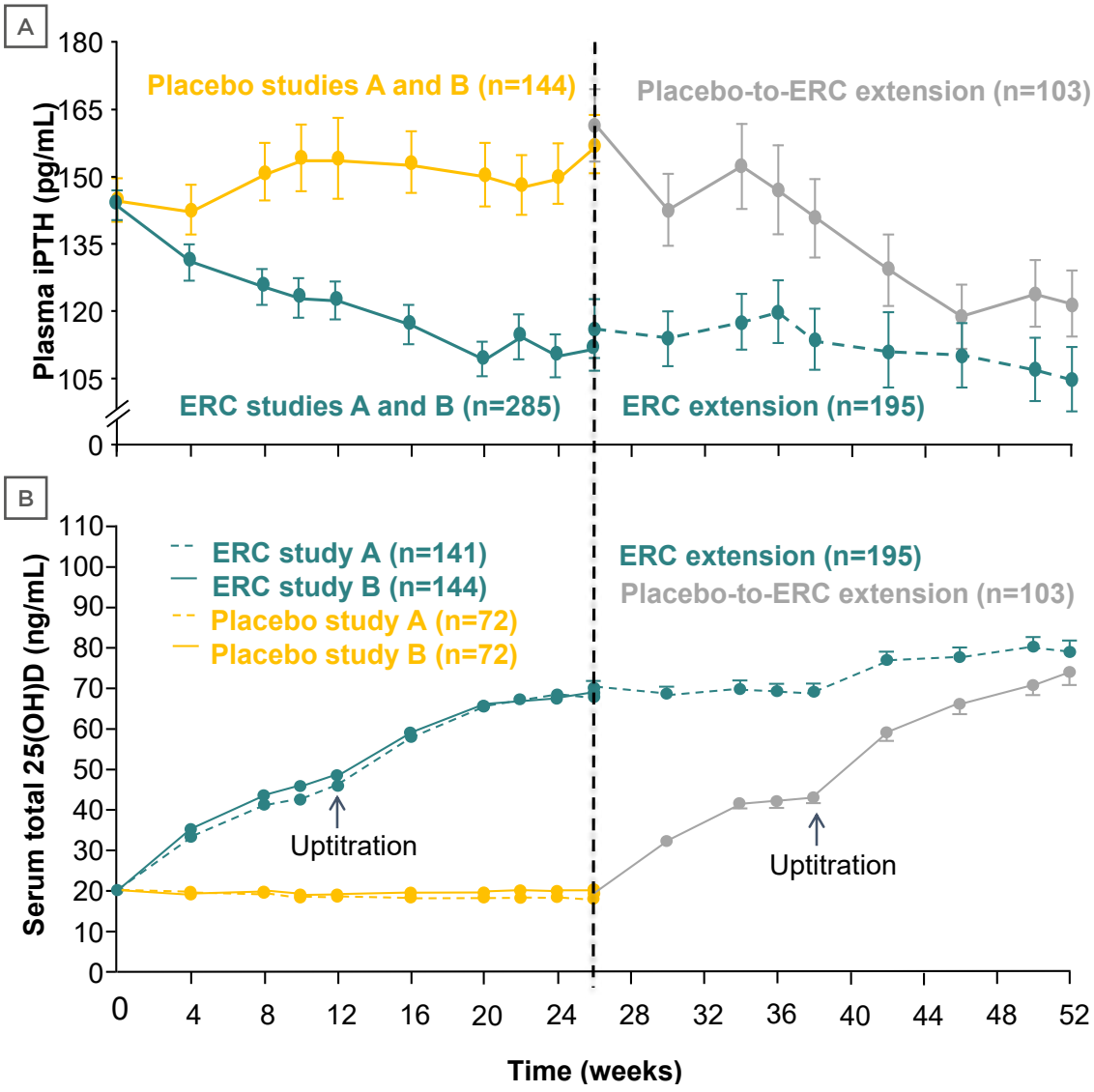


Figure 3: Mean standard error change over time in **A)** plasma-intact parathyroid hormone and **B)** serum total 25-hydroxyvitamin D (per protocol population).[18]

Note: Error bars are omitted for clarity in the first portion of the study.

ERC: extended-release calcifediol; iPTH: intact parathyroid hormone; 25(OH)D: 25-hydroxyvitamin D.

This decrease in iPTH was accompanied by an increase in 25(OH)D levels to 30–100 ng/mL[8] in patients treated with ERC; this was also achieved when placebo participants were switched to ERC (Figure 3B).[18] At Weeks 26 and 52, 25(OH)D levels were 50 and 59 ng/mL, respectively, for patients on the 30 µg dose of ERC, and 70 and 82 ng/mL, respectively, for patients on the 60 µg dose of ERC.[30]

Mean serum phosphorus levels were slightly greater in the ERC group, with a mean change from baseline of 0.2 mg/dL (standard error [SE]: 0.03) versus 0.1 mg/dL (SE: 0.04) in the placebo groups. Near-identical differences (0.2 mg/dL, SE: 0.02; versus 0.1 mg/dL, SE: 0.03) were shown for rises in serum calcium ($p<0.0001$). In the majority of patients, these increases had no clinical implications, with only one patient in the ERC group meeting the definition of hyperphosphataemia (two consecutive serum phosphorus values >5.5 mg/dL deemed study-related) and six participants in the ERC group who required dose reductions for hypercalcaemia (two consecutive serum calcium values >10.3 mg/dL). There were no significant differences between placebo and ERC or between ERC doses for serum FGF-23.[18,21]

Another finding of these studies (Figure 4) was that those with the highest 25(OH)D levels (mean: 92.5 ng/mL) had the greatest PTH suppression at Weeks 20–26 (to a mean of 97 pg/mL) and, conversely, those with the lowest 25(OH)D levels (mean: 13.9 ng/mL) had the least PTH suppression at Week 26 (mean: 166 pg/mL).[14] This, advised Germain, means that: "If you follow your vitamin D level, you can have a good indication of the efficacy you're going to get with ERC."

While clinical trials can reveal a lot of information about a drug, study participant limitations mean findings may not necessarily translate to a more general population. In a real-world setting, a retrospective analysis[31] was carried out of 174 patients with Stage 3–4 CKD, SHPT, and 25(OH)D insufficiency, of whom 173 received 30 µg daily ERC and one received 60 µg daily. This analysis found that after 12 months of ERC treatment, 70.1% of 122 analysed at this timepoint achieved 25(OH)D target levels of ≥30 ng/mL, with 40.2% of 70 patients analysed at this timepoint showing ≥30% reduction in PTH. There was little difference in calcium and phosphorus levels with continued ERC dosing in this cohort when analysed at a mean 27.8 and 28.8 weeks of follow-up, respectively.[31]

Conclusion

As SHPT manifests early in CKD and is associated with significant morbidity and mortality, it is a key feature of CKD that should be assessed and treated from the early stages of the disease.[2] Clinical studies show that people with CKD may require higher serum 25(OH)D target levels (>50 ng/mL) than those without CKD to achieve PTH reduction.[5,14,15] While SHPT can be managed by addressing vitamin D insufficiency, current approaches have limitations in that they either do not reliably and consistently lower PTH levels, as shown with cholecalciferol and ergocalciferol,[22] or they can increase hypercalcaemia risk, as shown with active vitamin D/analogues.[32] ERC can control SHPT by steadily increasing 25(OH)D levels over time, thus not inducing excess 25(OH)D catabolism, leading to lower PTH levels with minimal clinically relevant increases in calcium or phosphorus.[6,16,31]

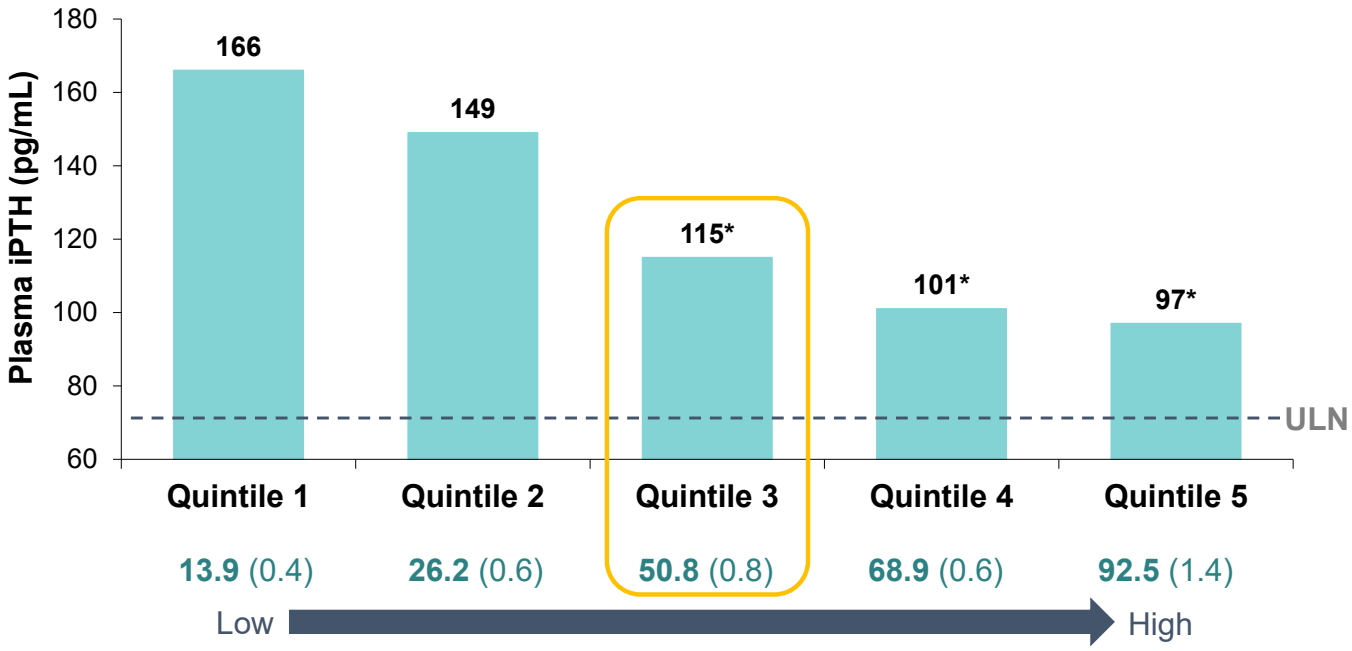


Figure 4: Plasma parathyroid hormone at Weeks 20–26 of treatment with extended-release calcifediol (30 or 60 µg) or placebo, as a function of post-treatment 25-hydroxyvitamin D quintiles (per-protocol population).[14]

*p<0.0001 versus quintile 1.

ERC: extended-release calcifediol; iPTH: intact parathyroid hormone; ULN: upper limit of normal; 25(OH)D: 25-hydroxyvitamin D.

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Idefirix® (Imlifidase): A Paradigm Shift in Transplanting the Untransplantable?

This symposium took place on 7th June as part of the 58th European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Virtual Congress

Chairperson: Uwe Heemann[1]

Speakers: Christian Morath,[2] Rainer Oberbauer,[3] Tomas Lorant [4]

1. Technical University of Munich, Germany
2. Heidelberg University Hospital, Germany
3. Medical University of Vienna, Austria
4. Department of Transplant Surgery, Uppsala University, Sweden

Disclosure: Heemann reported membership of advisory boards for Chiesi, Hansa, Hoffmann La Roche, and Vifor; and talks and chairmanships for AstraZeneca, Baxter, Chiesi, and Hansa Biopharma AB. Morath received funding for studies from FMC, E.N.D.I., DHS, BMWi, and BMBF; and is a shareholder and co-founder of TolerogenixX GmbH, a biotechnology company that develops new treatments for transplant and autoimmune indications. Oberbauer reported that Hansa Biopharma AB provided an honorarium for this talk. Lorant received a speaker fee from Hansa Biopharma AB to speak at the present symposium; and is a medical adviser to Hansa Biopharma AB.

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Meeting Summary

This symposium took place during the 2021 virtual meeting of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA). Heemann opened the session by highlighting the numbers of patients waiting for a kidney transplant and the proportion that will never receive an organ offer under the current system.

Morath defined the term untransplantable as highly sensitised (HS) patients with only a very small chance of receiving a crossmatch (XM) negative organ during allocation or when on a waiting list for organ allocation. These patients face extended times on waiting lists and are often removed from the list or die. Current organ allocation systems cannot fully address this issue, meaning that for some patients there is no hope of transplantation. There is a need for an alternative option that combines a special organ allocation scheme together with desensitisation options to remove donor-specific antibodies (DSAs), thereby increasing the chance of a donor organ offer.

Oberbauer outlined the current transplant options for HS patients, which are limited to live kidney paired exchange, acceptable mismatch, or desensitisation. Existing desensitisation protocols have demonstrated variable efficacy and the majority are only for use in a live donor setting.

Lorant introduced Idefirix® (imlifidase) as a new option for desensitisation of adult patients with positive XM against a deceased kidney donor. He highlighted results from clinical trials that showed that imlifidase treatment rapidly inactivated DSAs and converted positive XMs into negative, with 2 year patient and graft survival of 90% and 82%, respectively.

How Can We Transplant Highly Sensitised Patients?

Uwe Heemann

Germany alone has approximately 7,000 people waiting for a kidney transplant. In 2020, there were nearly 600 HS patients on the waiting list (5.5% of listed patients) and nearly 280 transplantable patients in the Eurotransplant Acceptable Mismatch (AM) programme.[1]

There are patients in the AM programme who cannot be transplanted at present. The EUROSTAM initiative investigated the possibility of transplanting all comers, including HS patients. An analysis of the Eurotransplant database, including the UK, Spain, Czech Republic, and Greece in 2012–2015, identified 700 patients who were not transplantable.[2] If the AM programme of Eurotransplant was enlarged, 25–30% would benefit but 400 patients would still never receive an organ offer. This translates into 0.5% of those waiting for a transplant never receiving an organ offer, making it clear that help is needed. This symposium addressed the question "Is imlifidase the solution we need?" in three talks.

Defining the Untransplantable

Christian Morath

Untransplantable refers to HS patients with only a small chance of getting a XM negative organ during organ allocation. Traditionally, these patients were defined by a panel reactive antibody (PRA) of ≥85%. But more recently, with the introduction of virtual PRA (vPRA), patients with vPRA ≥95–98% were considered strongly disadvantaged and potentially untransplantable.

Examination of the Heidelberg waiting list revealed that 9.1% of patients had vPRA >85% and 6.3% had vPRA >95%, which represents a considerable proportion of the total waiting list. These are highly disadvantaged patients. Two case reports with vPRA ≥99% illustrate this point; both had a very low donor frequency (0.044% and 0.160%) and had been waiting for 16 and 10 years, respectively. These patients will never be transplanted unless additional measures are taken, such as desensitisation.

Looking at the broader Eurotransplant area, there are special initiatives for HS patients such as the AM programme. In the past, patients with a PRA >85% were transplanted with high priority. This programme helps to avoid long waiting times in sensitised patients and is associated with good graft survival rates in transplanted patients.[3] A study in 2018 showed that graft survival rates at 10 years for patients in the AM programme (n=869) were similar to patients with PRA 6–85% (n=12,289) but better than those with PRA >85% (n=1,866) transplanted outside the AM programme.[1] However, two points should be considered. First, patients transplanted in the AM programme in this analysis had a current PRA of only 26%, indicating that they were perhaps not the most disadvantaged. Second, the analysis only included patients who were successfully transplanted. There were no data on patients who were placed on the AM but received no donor organ.

The study leads to the question: what are we currently looking at and what should we be looking at? Currently, we are looking at graft survival rates of patients who received a kidney transplant. Just 57.6% of patients placed on the AM waiting list during the last 28 years received a successful transplant.[4] However, 42.4% of AM patients were not transplanted. We should be looking at patient survival rates of patients placed on the waiting list rather than survival rates of those who received a transplant.

What happened to the patients who were not transplanted? The EUROSTAM project provides a picture of the fate of these patients. The project compared access to transplantation for HS patients from the local donor population (e.g., Eurotransplant) versus a larger donor pool comprising different partner organisations of Eurotransplant (i.e., the UK, Spain, Greece, the Czech Republic). For this simulation, 722 patients were identified from the five organisations with ≥95% sensitisation and a waiting time >5 years (i.e., the untransplantable patients). Even with broadening the donor pool, 73% of patients had no greater chance of getting a compatible organ offer.[5] These data illustrate that the problem extends beyond Heidelberg and that across Europe many patients accumulate on the waiting list without a realistic chance of an organ offer unless additional measures such as desensitisation are taken.

Looking into the situation in the USA, there was some improvement in 2014 after implementation of the kidney allocation system (KAS). For HS patients, there was a steep increase in the transplantation rate from around 2–3% to 17%.[6] However, 34% of HS patients have a calculated PRA (cPRA) of ≥99.95% and these patients did not benefit from implementation of the KAS with transplantation rates of only 8%. This group makes up a considerable proportion of the waiting list, with 5.5% of the total list having a cPRA of 100%.[7] These patients are mostly younger (48.0 years), more likely retransplant recipients (71.8%), and are more likely to have longer waiting times (4.3 years). This illustrates that in the USA, there is also a considerable proportion of patients who need additional measures such as desensitisation to obtain access to kidney transplantation.

What happens to patients with no realistic chance of getting a kidney transplant and a suitable organ offer? An analysis of waiting times in the UK stratified by calculated reaction frequency (cRF) levels showed that most patients wait <7 years.[5] However, if the cRF value is >95%, patients wait up to 35 years. Data from the USA illustrate that only a very small proportion of patients (<10%) with very high cPRA (>99.9%) are transplanted.[7] The data show that most patients persist on the waiting list, and are then removed or die.

More than 50% patients with cPRA >99.9% have been on the waiting list for >5 years compared to 10% of those with cPRA <80%.[7] In an analysis of mortality stratified by cPRA before and after implementation of the KAS programme, mortality rates up to 3 years were similar for all cPRA categories except 99.9%+ which continued to have a higher mortality rate compared to all other groups.[8]

Most HS patients cannot be transplanted by kidney allocation alone and need additional measures. Data from the USA show that increased anti-HLA DSA strength was associated with worse graft outcomes and higher mortality following live donor kidney transplantation.[9] Desensitisation therapy conferred a survival advantage compared to dialysis or transplantation or dialysis alone.[10] In the desensitisation group, the Kaplan–Meier estimate of patient survival was 80.6% at 8 years, compared with 49.1% in the dialysis or transplantation group and 30.5% in the dialysis only group (p<0.001 for both comparisons).

The combination of a special allocation programme, such as the AM programme, and desensitisation is a strategy that can lead to transplantation and good results. The introduction of an integrated algorithm in Heidelberg in 2006–2007 led to improved graft survival.[11,12] Graft survival in sensitised patients was equal to that of unsensitised patients. In addition, many patients who were transplanted following pre-transplant desensitisation would otherwise have persisted on the waiting list for an indefinite period of time.

In summary, all available measures are needed to transplant the (untransplantable) patients with very high PRA who make up a considerable proportion of those on the waiting list. These patients need special allocation together with desensitisation.[13] Unfortunately, most of these special programmes/measures (e.g., kidney paired donation) are not permitted in Germany.

Pathways to Transplant the Positive Cross-Match Highly Sensitised Patients

Rainer Oberbauer

For very HS patients and those without living donors, a strategy of desensitisation offers the best hope of transplantation.[14] It has been calculated by Keith et al. that to achieve a 95% probability of finding an acceptable donor, a candidate with a cPRA of 99.99% would need to be part of 30,000 potential donor match runs.[15] The probability of finding an acceptable match is calculated as 1-(cPRA)n where n is the number of potential donors. To achieve a 95% chance of finding an acceptable match, a candidate with a cPRA of 95% would need to be part of 59 donor match runs. This means that if 59 blood group compatible (e.g., blood group O) donors are available per year then it is reasonable to have these patients in an AM programme. HS patients also have a very low chance of transplantation through a paired exchange programme, and, for these patients, desensitisation is the only realistic way to proceed.

A simulation of chances for match in a kidney paired donation programme stratified by cPRA demonstrated that most matches, even in the low sensitised patients, occur in the first 3 months.[16] After this period, the number of candidates remains fairly constant.

There is some evidence showing a survival benefit from desensitisation and transplantation with a kidney from an incompatible living donor. A multicentre study from the USA demonstrated that patients who underwent desensitisation therapy and received kidney transplants from HLA-incompatible living donors had a substantial survival benefit compared with those who did not undergo transplantation and those who waited for transplants from deceased donors.[17] However, a similar analysis from the UK found no survival benefit.[18] Possible explanations for the discordant findings include different definitions of desensitisation, use of different matching methods, and different patient populations between the two studies.[19]

The most common desensitisation protocols typically non-specifically remove circulating DSA with plasmapheresis, immune absorption, or plasma filtration. In addition, the production of antibodies can potentially be inhibited by drug combinations while single drug combinations have not been shown to be successful. Desensitisation protocols have been developed based on experienced rather than on solid clinical trials since the number of patients in need of such a procedure is rather limited.

The pharmacological targets of humoral response in organ transplantation have been illustrated by Kwun and Knechtle.[20] The interaction of follicular helper cells with B cells in the lymph node can be inhibited by established therapies such as costimulation blockade and anti-B cell therapies. Plasma cells can be depleted with drugs from the myeloma field such as anti-CD38 antibodies or second or third generation proteasome inhibitors. Further targets include the unspecific removal of antibodies from the circulation and the inhibition of the complement cascade although this has not been proven to be useful for desensitisation.

A recent study in a 25-centre cohort using Scientific Registry of Transplant Recipients (SRTR) linkage showed that the risk of biopsy-confirmed acute rejection (AR) increased with sensitisation.[21] AR developed in 8.4% of compatible live donor kidney transplantation, 18.2% of positive Luminex, negative flow XM, 21.3% of positive flow, negative cytotoxic XM, and 21.7% of positive cytotoxic XM recipients.

Incompatible living donor kidney transplantations without biopsy-confirmed AR exhibited an even lower risk of graft loss as compared to compatible live donor transplants with subsequent biopsy-confirmed AR. So not unexpectedly, incompatible living donor transplants with AR had the worst results, with approximately 40% rate of graft loss at 10 years after transplantation. The findings demonstrate that biopsy-confirmed AR is an important effect modifier in that setting.

What can be done to prevent the reappearance of DSA and antibody-mediated rejection (AMR)? Dual targeting is an appealing strategy, targeting the follicular helper cell and B cell interaction with costimulation blockade and at the same time inhibiting plasma cells with proteasome inhibitors, for example.[20]

This approach has been tested in a non-human primate model of kidney transplantation.[22] The authors evaluated carfilzomib (CFZ), a second-generation proteasome inhibitor, plus the costimulation blocker lulizumab (CD28dAb), a CD28 domain antibody antagonist that selectively targets the CD28-CD80/86 interaction and preserves the co-inhibitory signal (CTLA4-CD80/86). Four weeks of perioperative desensitisation with CFZ and CD28dAb reduced DSA levels compared to untreated controls by approximately 50%. This combination also reduced follicular helper cells and proliferating B cells in the lymph node after desensitisation. CFZ and lulizumab did not prevent DSA rebound as early as 2 weeks after engraftment. The combination prolonged graft survival and prevented AMR initially; however, after 3 months all grafts failed due to AMR.

In summary, HLA-incompatible transplants lead to a broad alloimmune response as evidenced by a mixed lymphocyte reaction before transplantation, high PRAs, and potentially non-HLA alloimmunity. Thus, many branches of the humoral cascade need to be targeted. Desensitisation is a strategy for a minority of live

donor kidney transplants but is the only chance of a transplant for HS patients. Imlifidase may be an option in such situations.

Idefirix® (Imlifidase): A New Treatment Option

Tomas Lorant

Desensitisation is an effective technology that could be considered in selected patients. HS patients typically have elevated levels of numerous HLA antibodies and transplantation requires long-term removal of these antibodies.

It has been demonstrated that patients with high pre-transplant levels of DSAs have worse outcomes (e.g., lower likelihood of graft survival) after transplantation compared to those with low levels of DSAs.[23] Activation of the complement cascade is involved in AMR. It has been demonstrated that patients with complement-binding DSAs after transplantation had the lowest 5-year rate of graft survival (54%), compared to patients with non-complement-binding DSAs (93%) and patients without DSAs (94%).[24]

Data from the USA suggest that HLA-incompatible live donor kidney transplantation may improve patient survival compared to remaining on the waiting list or waiting for a compatible deceased donor kidney.[17] This indicates that in these cases, if there is an available HLA-incompatible kidney, desensitisation followed by transplantation could be of potential benefit.

Imlifidase is an immunomodulatory streptococcal protease agent that cleaves all forms of IgG in a 2-step process.[25-27] IgG is cleaved at the lower hinge region to form $F(ab')_2$ and Fc fragments. Imlifidase is highly specific for IgG, and other molecules (i.e., IgA, IgD, IgE, and IgM) are not cleaved. IgG cleavage leads to inactivation of all IgG-dependent Fc-dependent effector functions, including antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity.[25-29]

A number of clinical studies have been conducted with imlifidase. In a Phase I study of 29 healthy subjects, imlifidase was able to inactivate Fc-mediated effector functions *in vivo*, was considered safe with no serious adverse events, and there was no dose limiting toxicity.[25] This research was followed by four Phase II clinical studies in kidney transplant recipients.[30-33]

The first transplant was performed in a patient with a positive serum XM (HLA-B7). After imlifidase infusion, when an HLA-incompatible (HLA-B7+) kidney from a deceased donor was offered, the HLA antibody profile was negative, and the kidney was transplanted successfully.[30] Stable graft function was maintained for >36 months with normal creatinine clearance, no proteinuria, and no rejection episodes.

Jordan et al. reported the combined experience of two independently conducted open-label, Phase I–II trials assessing the efficacy of imlifidase for desensitisation and kidney transplantation from an HLA-incompatible donor.[31] A total of 25 highly HLA-sensitised patients (11 in Sweden and 14 in the USA) received imlifidase before undergoing transplantation with a kidney from an HLA-incompatible donor. Total IgG and HLA antibodies were eliminated at transplantation. Perfusion of allografts after transplantation was achieved by 24 patients. AMR occurred in 10 patients (3 in Sweden and 7 in the USA) at 2 weeks to 5 months after transplantation, but all of these patients had a response to treatment. There was 1 graft loss, which was mediated by non-HLA IgM and IgA antibodies. The authors concluded that imlifidase reduced or eliminated DSAs and permitted HLA-incompatible transplantation in 24 of 25 patients.

The Highdes trial (15-HMedIdeS-06)[33] was focused on very HS patients. This was an open-label, single arm, Phase II trial conducted at five centres in the USA, Sweden, and France. The primary efficacy endpoint was the ability of imlifidase to convert a positive to a negative XM test within 24 hours after dosing. A total of 18 patients were enrolled. DSA were present in all patients and the median cPRA was 99.83%. The majority of transplanted patients (89.5%) demonstrated conversion of baseline positive XM to negative within 24 hours after treatment with imlifidase. DSA usually rebounded 3–14 days after imlifidase therapy, although there

was substantial interpatient variability. At 6 months, patient survival was 100% and graft survival was 88.9%. AMR occurred in 38.9% patients, with an onset 2–19 days post transplantation. Of 237 total treatment-emergent adverse event, seven (occurring in six patients) could be attributed to imlifidase.

Regarding long-term follow-up, a prospective, observational, 5-year study is currently ongoing in 46 HS patients who received kidney transplants after desensitisation with imlifidase.[34] This study will provide data on parameters such as patient and graft survival, comorbidity, treatment of graft rejection episodes, quality of life, and anti-drug antibody levels and runs until December 2022.[35]

Two-year results in 31 patients demonstrated a survival rate of 91% (31 of 34 patients).[34] The three deaths all occurred in the positive XM population (i.e., the most complex patients) at 7–12 months post-transplantation and were not related to imlifidase treatment. At 2 years, death-censored graft survival was 90% while graft failure-free survival was 82%. Graft loss in some patients was linked to reduction of immunosuppression, some patients had problems with infections and one patient completely stopped his immunosuppressive medication.

Early AMR (onset during the first month post-transplant) occurred in 28% of XM positive patients, while another 10% were identified as late AMR; only one AMR occurred later than 6 months after transplantation. Most AMRs were not recurring. The majority of patients (92%) had satisfactory or good kidney function (≥30 ml/min/1.73m^2), and at 2 years the median estimated glomerular filtration rate was 61.5 ml/min/1.73m^2 (range: 22.4–106.7 ml/min/1.73m^2).

In summary, across all Phase II trials imlifidase treatment rapidly inactivated DSAs and converted positive XMs into negative. Rebound is expected in all cases, leading to AMR in some, but not all, patients. AMR incidence was consistent with expectations and aggressive treatment of AMRs is a key factor for successful long-term graft survival. At 6 months post-transplantation, 94% of patients had functioning grafts and were off dialysis. There were no graft losses due to IgG-mediated AMR. The safety profile of imlifidase treatment was consistent with that expected in a kidney transplantation population.

Imlifidase was granted a conditional marketing authorisation by the European Commission in August 2020 for "desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor."[36] This milestone launched a new era in kidney transplantation for selected patients who would previously have remained untreated.

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Abstract Reviews

Sharing insights and updates from a selection of abstracts presented by leading experts in the field of nephrology at the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA)

Nephrotoxic Mechanisms of Gadolinium: Implications for the Use of Gadolinium-Based Contrast Agents

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Keywords: Gadolinium, gadolinium-based contrast agents, inflammation, lipid deposition, mitochondrial dysfunction, nephrotoxicity, oxidative stress.

Citation: EMJ Nephrol. 2021;9[1]:46-47. Abstract Review No. AR1.

BACKGROUND AND AIMS

Gadolinium-based contrast agents are widely used for MRI. Although they may be considered well-tolerated at recommended dosing levels, recent evidence supports the deposition of free gadolinium in the tissues and its slow release into circulation, resulting in long-term toxicity, which is aggravated in renal patients.[1,2] The kidney, as the major excretion organ of these agents, and particularly the proximal tubule, is a common location of xenobiotics' bioaccumulation;[3,4] therefore, the kidneys may be key targets of gadolinium's deleterious effects. This study aimed to unveil the nephrotoxic potential and the underlying mechanisms of toxicity of gadolinium, using an *in vitro* model of normal human adult proximal tubular cells (HK-2 cell line).

MATERIALS AND METHODS

HK-2 cells were exposed for 24 hours to a wide concentration range of ionic gadolinium in the form of trichloride hexahydrate, and cell viability was assessed to estimate the half-maximal effective concentration (EC_{50}) and the sub-toxic concentration eliciting 1% of cell death (EC_{01}). These ECs were further used to determine the concentration-dependent effects of gadolinium in this renal cell model: oxidative stress, mitochondrial (dys)function, cell death mechanisms, lipid deposition, and inflammatory response.

RESULTS

Gadolinium induced cell death in a concentration-dependent manner, with estimated EC_{01} and EC_{50} of 3 and 340 µM, respectively. When compared to control cells, the subtoxic concentration showed no significant effects in reactive oxygen and nitrogen species (ROS and RNS) production, total glutathione levels or total antioxidant status. On the other hand, the EC_{50} showed significant disruption of the oxidative status of the cell, with >60% depletion of total glutathione levels cell contents ($p<0.01$) and a significant decrease of total antioxidant status ($p<0.05$). However, this effect was not accompanied by an increase, but rather by a significant decline, in ROS and RNS production of about 50% below control ($p<0.0001$). At the EC_{50}, but not at EC_{01}, a disturbance of the mitochondrial and energetic homeostasis was also observed, as shown by the increment of intracellular free calcium levels, hyperpolarisation of the mitochondrial membrane, and decay of the ATP levels ($p<0.0001$). Cell death induced by gadolinium was characterised by typical morphological changes of both apoptosis and necrosis, with a significant increase in propidium iodide uptake and lactate dehydrogenase leakage ($p\leq0.0001$) at EC_{50}. The presence of neutral lipids-containing vesicles was observed in the cytoplasm of cells exposed to gadolinium, already noticeable at the sub-toxic concentration. Cells exposed to gadolinium also showed increased expression of the pro-inflammatory gene *IL6*, though this effect was only significant at the EC_{01} ($p<0.05$).

CONCLUSION

Gadolinium showed a marked cytotoxic potential at micromolar levels in HK-2 cells. This cytotoxicity was characterised by increased oxidative stress, independent of ROS and RNS production, and mitochondrial dysfunction followed by cell death via apoptosis and, ultimately, by necrosis. At a sub-toxic concentration, gadolinium was also able to elicit the accumulation of lipidic vesicles within the cells' cytoplasm, and to trigger a pro-inflammatory response. Although it is still unclear which amount of gadolinium is in fact released from the complexes commonly used as contrast agents, this study shows that the gadolinium ion has direct nephrotoxic potential, with noteworthy impact at sub-toxic concentrations. ■

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'Sweet Hypoxia' with Acute Kidney Injury: The Unpredictability of Acute Hypoxic Respiratory Failure in COVID-19 Infection – a Community Hospital Experience

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Keywords: Acute hypoxic respiratory failure, acute kidney injury, chest radiograph, COVID-19, dyspnoea, mechanical ventilation, sweet hypoxia.

Citation: EMJ Nephrol. 2021;9[1]:48-49. Abstract Review No: AR2.

INTRODUCTION

Severe COVID-19 infection may result in hypoxaemic respiratory failure, necessitating invasive mechanical ventilation.[1-3] The authors revisited the phenomenon of asymptomatic patients despite very low pulse oximetry readings, the so-called 'sweet hypoxia', 'happy hypoxia', or 'silent hypoxaemia'.[4-6] This abstract review describes, for the first time, the sequential chest radiographic images representing the progressive radiological trajectory of COVID-19 pneumonia.[7]

CASE REPORT

A 62-year-old Caucasian male who was obese, hypertensive, and an ex-smoker, was diagnosed with mild community-acquired pneumonia in mid-March 2020, following evaluation for low-grade fever. He had travelled to Florida and Texas, USA, in the previous month.[7] He tested positive for COVID-19 by reverse transcription PCR. One week later he was admitted to a community hospital with a 1-day history of new shortness of breath and loose stools. Chest radiograph revealed new patchy left lower lobe air-space infiltrate (Figure 1B). Treatment included nasal cannula oxygen, intravenous fluids, intravenous azithromycin, and intravenous ceftriaxone. He improved and was discharged the next day on azithromycin (500 mg per day for 3 days) and cefdinir (300 mg twice daily for 5 days).

He was readmitted approximately 18 hours post-discharge with worsening dyspnoea. Chest radiograph showed worsening bilateral infiltrates (Figure 1C) and he soon required emergent intubation in the emergency department (Figure 2A). He was transferred to the intensive care unit on intravenous vancomycin and intravenous cefepime. He developed septic shock and required intravenous norepinephrine. With worsening chest radiographs (Figures 2B and 2C), he was subsequently transferred to a tertiary medical centre. Intravenous azithromycin (500 mg daily) and intravenous ceftriaxone (2 g daily) were administered for 8 days. Chloroquine phosphate (500 mg twice daily) was added. Intravenous norepinephrine was continued. He was extubated after 4 days and discharged home after 9 days, with normalised creatinine of 1.03 mg/dL.[7]

DICSUSSION AND CONCLUSIONS

The authors have, for the first time, demonstrated in meticulous and real-time details the sequential chest radiographic images of the changes of the progressive radiological trajectory of COVID-19 pneumonia.[7] The place of non-invasive ventilation demands further study.[8-10] The so-called 'sweet hypoxia' or 'happy hypoxia' or 'silent hypoxaemia' in COVID-19 is revisited; indeed, it is not limited to patients with COVID-19.[3,5] The need to mitigate lung barotrauma is mandatory.[8-10] Finally, prognostication of pneumonia in COVID-19 is unpredictable.[7] Premature discharge from the hospital is strongly discouraged.[7]■

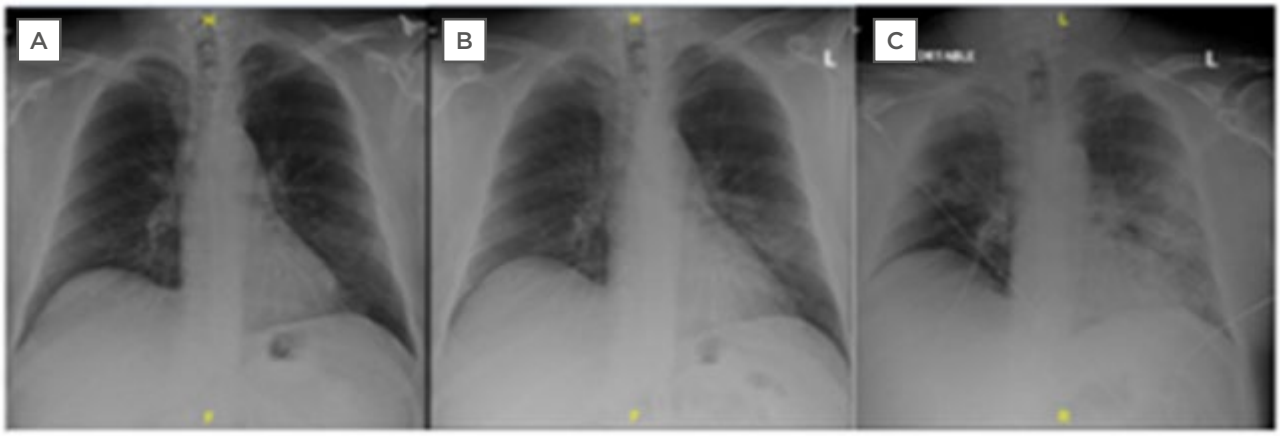

Figure 1: Sequence of chest radiographs. A) Normal in November 2019. **B)** Before initial hospital admission (20th March 2020, at 2:10:10). **C)** Just prior to intubation in the emergency department following the second admission (22nd March 2020, at 3:32:01).

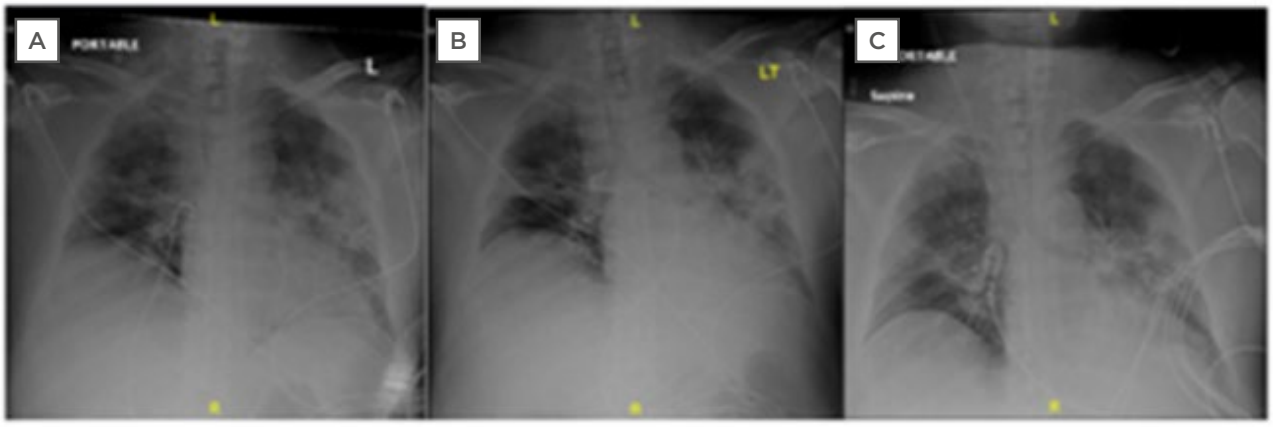

Figure 2: Series of chest radiographs following intubation in the emergency department. A) 22nd March 2020, at 4:27:11. **B)** Half an hour post-intubation (22nd March 2020, at 5:08:38). **C)** Approximately 4 hours post-intubation in the intensive care unit before transfer (March 22nd 2020, at 8:10:30).

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Leptospirosis and Hyponatraemia

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Keywords: Acute kidney injury (AKI), hyponatraemia, leptospirosis.

Citation: EMJ Nephrol. 2021;9[1]:50-51. Abstract Review No. AR3.

BACKGROUND AND AIMS

Leptospirosis is a zoonosis of importance for public health that occurs in endemic form in Brazil.[1-3] Acute kidney injury (AKI) is part of its severe form, associated with haemorrhagic manifestations and hepatic dysfunction. Hydroelectrolytic disorders are described and are associated with tubular dysfunction caused by direct effects of leptospira.[4,5] In this study, the authors investigated the occurrence of hyponatraemia, which is known to complicate the course of several infectious diseases.

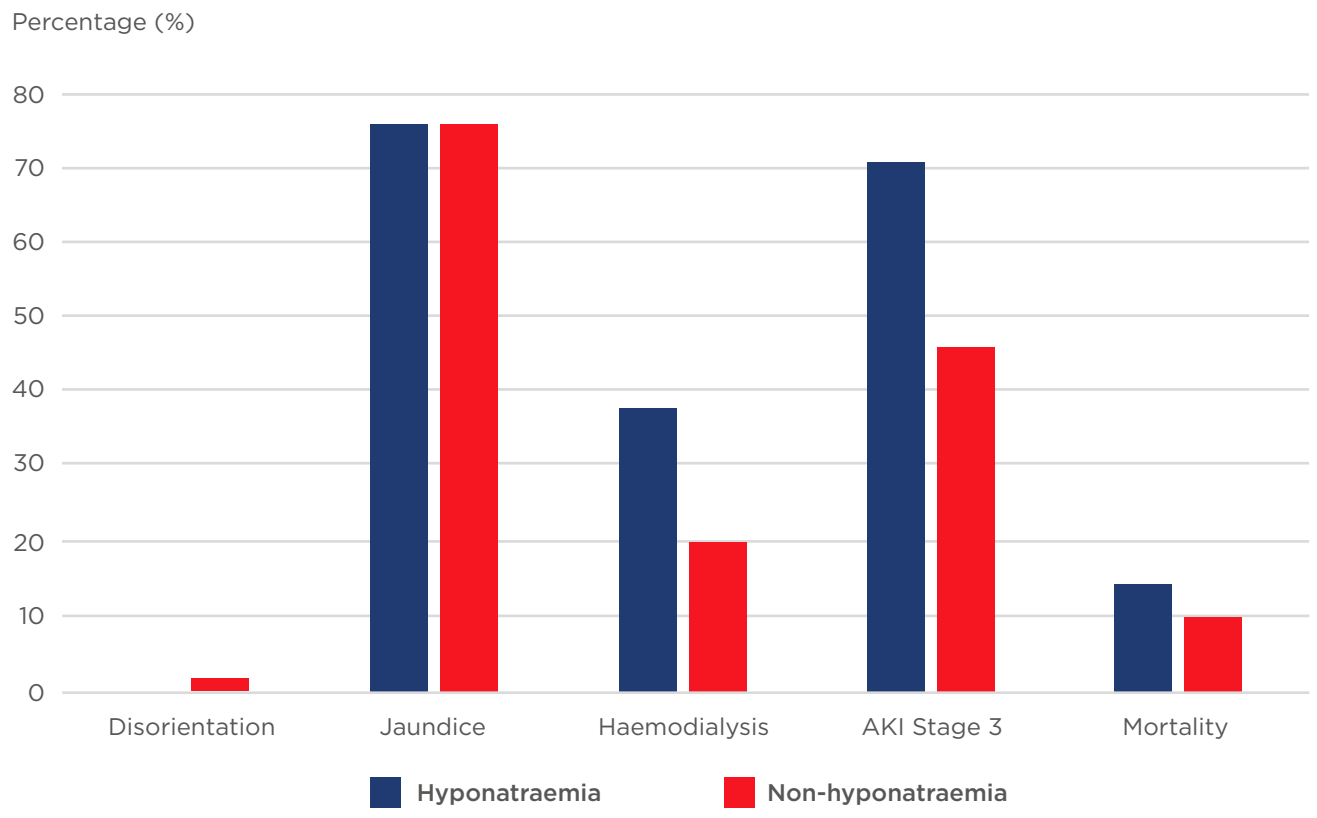

Figure 1: Comparison of patients with leptospirosis according to the presence of hyponatraemia in Fortaleza, Brazil.
AKI: acute kidney injury.

MATERIALS AND METHODS

This study is part of a cohort of patients with leptospirosis from Fortaleza, northeast Brazil, from 1985 to 2018, admitted to tertiary hospitals with the severe form of the infection (Weil's disease). Two groups of patients were compared according to the levels of serum sodium: <135 mEq/L (which was considered as hyponatraemia); and >135 mEq/L and <145 mEq/L (which was considered the normal range). A total of 319 patients were included in this analysis, which had sodium dosage at hospital admission. Patients' mean age was 37±15 years, and 84% were male.

RESULTS

Hyponatraemia was found in 163 cases (51%) at hospital admission. Patients with hyponatraemia had more severe symptoms, like disorientation (8.1% versus 1.3%; p=0.047) and jaundice (76% versus 54%; p≤0.001), and higher levels of urea (130±80 versus 94±34 mg/dL; p≤0.001) and creatinine (4.3±2.7 versus 3.0±2.6 mg/dL; p≤0.001). They also had a higher frequency of complications, such as need for haemodialysis (38% versus 20%; p≤0.001) and AKI Stage 3 (71% versus 46%; p=0.002). Regarding mortality, there was a slight increase in the rate of death (Figure 1) among those with hyponatraemia (14.1% versus 10.1%), but not statistically significant (p=0.281).

CONCLUSION

Hyponatraemia is a frequent complication in leptospirosis, associated with a more severe disease, which should be treated early to avoid fatal outcome. The pathophysiology certainly includes renal tubular abnormalities, but the exact mechanisms should be further investigated. ■

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Spontaneous Renal Artery Dissection: Is It Really So Rare?

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Keywords: Acute renal infarction, anticoagulation therapy, CT angiography, renal artery dissection.

Citation: EMJ Nephrol. 2021;9[1]:51-53. Abstract Review No. AR4.

BACKGROUND AND AIMS

Spontaneous renal artery dissection (SRAD) is a rare and often unrecognised clinical entity, which accounts for 1–2% of all arterial dissections. It can be the result of several underlying diseases, such as atherosclerosis, malignant

hypertension, fibromuscular dysplasia, and connective tissue disorders.[1] Even though atherosclerosis is considered the principal cause of SRAD cases, the aetiology of the majority of cases remains unknown.

There are three different clinical manifestations: sub-acute state without apparent progression; renal infarction state due to an acute occlusion; and chronic state with renovascular hypertension. Renal infarction due to SRAD is often misdiagnosed as acute pyelonephritis, which can cause delays in the diagnosis and treatment.

MATERIALS AND METHODS

The authors discuss five patients with renal infarction due to SRAD who were admitted to their unit in the prior 1.5 years. There were three males and two females, with a mean age of 50±7.8 years.

From the onset, all patients presented sudden-onset flank pain and new-onset hypertension, and were referred to the authors' unit at least 1 week later. At admission, renal function was normal for all patients, but two presented microhaematuria. Blood tests showed leukocytosis, high C-reactive protein and fibrinogen levels, and hyperhomocysteinaemia.

Two males had a family history of cardiovascular disease. Moreover, one was diagnosed with a gastrointestinal stromal tumour, and the other was diagnosed as OFP ostium II. The third male had family history of malignancy. One female had a history of kidney stones and the other had dolichocolon. Abdominal CT angiography (CTA) showed renal infarction due to SRAD, which was bilateral in two patients (Figure 1A).

All patients were treated with anti-hypertensive drugs and systemic anticoagulation (two with continuous intravenous heparin infusion and three with subcutaneous low-molecular-weight heparin), followed by oral warfarin.

RESULTS

At the 3-month follow-up, all the patients had become normotensive and partial or total renal artery recanalisation was found (Figure 1B). All patients had a work-up for hypercoagulable state (activated protein-C resistance, protein S, antithrombin III, antiphospholipids and anticardiolipin antibodies, lupus anticoagulant, and Factor II and V mutation) and for immunological disorders (anti-nuclear antibody, anti-neutrophil cytoplasmic antibodies, complement levels, rheumatoid factor, Ig), all of which were within normal limits or negative, except in one patient who presented a Factor II mutation.

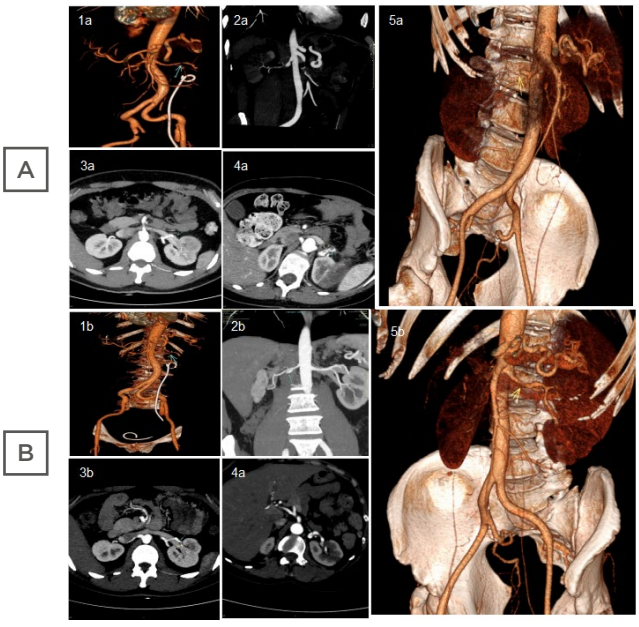

Figure 1: Spontaneous renal artery dissection in five patients at A) onset and B) after 3 months of anticoagulant therapy.

Molecular genetic testing for hereditary aortic diseases and related disorders of connective tissue were performed; one patient was negative, the patient with Factor II mutation showed *COL5A1* c.514G>T (heterozygous) mutation, and testing in the three remaining patients is still ongoing.

In literature, over 200 SRAD cases have been reported: one-quarter on autopsy, mostly males (4:1 ratio) in their late 40s to early 50s, usually without any underlying disease, and with bilateral involvement in 10–15% of cases.[2] SRAD was most commonly diagnosed by CTA or magnetic resonance angiography. Invasive exploration with angiography is only recommended at an early stage to determine the extent of the lesion and whether endovascular treatment is feasible. The efficacy of oral anticoagulation and anti-hypertensive medication is still controversial. Due to late referral to the authors' unit, invasive exploration with angiography was not performed; abdominal CTA was diagnostic, and conservative medical treatment was effective in all patients.

CONCLUSION

To summarise, renal infarction due to SRAD seems to be more common than expected in young and healthy patients without apparent underlying disease. Non-invasive procedures and 3-month conservative medical treatment are safe and effective, while molecular genetic testing could be helpful to reveal possible predisposing factors. ■

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Senescence-Like Changes in B-Cell Phenotype in Patients with Haemodialysis

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BACKGROUND AND AIMS

Patients on dialysis are characterised by susceptibility to infections, high prevalence of cancer, cardiovascular disease, and poor response to vaccinations,[1,2] conditions met mostly in aged individuals. Compromised immune function seen in end-stage renal disease (ESRD) is demonstrated by profound immune cell phenotype changes and might be a primary cause for the above-mentioned conditions. These alterations resemble the natural course of senescence, and are, therefore, termed immunosenescence. Whereas alterations of T cells in ESRD have been studied to a certain extent,[3] the data concerning the B-cell subpopulation are, to the present, insufficient. The purpose of this study was to evaluate the effects of haemodialysis (HD) on B-cell subsets, in terms of untimely expression of immunosenescent phenotype.

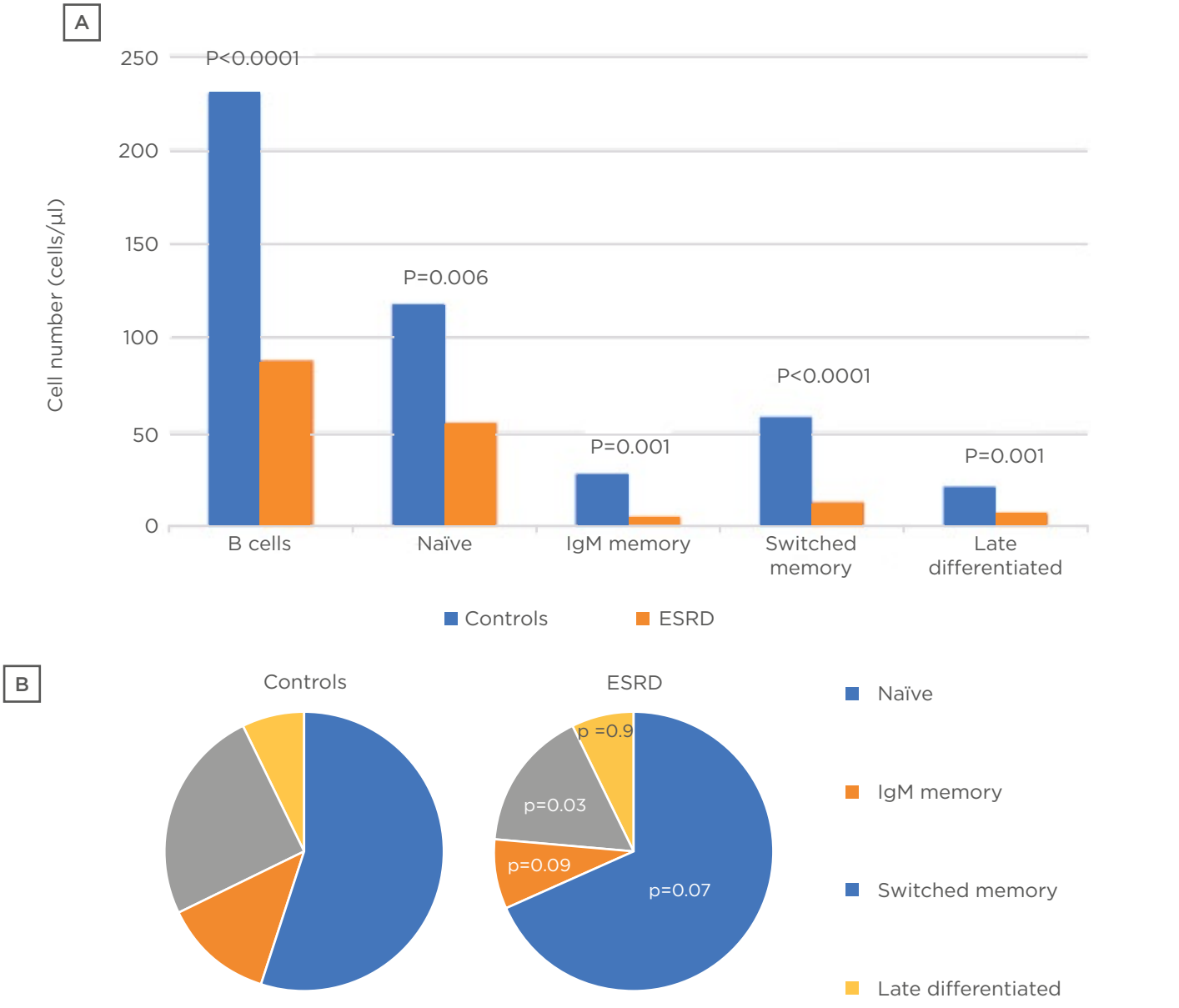

Figure 1: A) B-cell subset counts in healthy controls and ESRD; and B) B-cell subset percentages in healthy controls and ESRD.

ESRD: end-stage renal disease; NS : non-significant.

MATERIALS AND METHODS

B-cell phenotype was analysed by flow cytometry in 25 patients with ESRD on HD (15 males and 10 females; mean age: 59±14.7 years). Patients on HD with systemic diseases, malignancy, or a recent (<3 months) episode of infection were excluded. A sample of total blood was collected from the patients before initiation of a mid-week routine dialysis session. A total blood count was performed according to standard methods and a fresh blood sample, with dipotassium ethylenediaminetetraacetic acid for anticoagulation, was analysed with flow cytometry. Subpopulations, including naïve (IgD+CD27-), IgM memory (IgD+CD27+), switched memory (IgD-CD27+), and late memory (IgD-CD27-) B cells were determined. Findings were compared to 12 healthy controls of similar age.

RESULTS

A severe B lymphopenia was observed in patients on dialysis in comparison to healthy controls, affecting both the percentage (6.5±2.7% versus 11.9±4.5%; p<0.0001) and absolute count of B cells (88 [53] versus 229 [271] cells/µL; p<0.0001). A decrease in absolute numbers (Figure 1A) was also seen in all four subsets of B cells (naïve 55 [54] versus 118 [216] cells/µl, p=0.006; IgM memory 5 [11] versus 28 [25] cells/µL, p=0.001; switched memory 13 [10] versus 59 [64] cells/µL, p<0.0001; late memory 7 [7] versus 21 [24] cells/µL, p=0.001). However, whereas naïve, IgM memory, and late memory B cell proportions were similar between patients and controls, switched memory B cell percentage showed a significant decline (Figure 1B) in the dialysis cohort (15.7 [11.7]% versus 25.7 [18.9]%; p=0.03).

CONCLUSION

B-cell numbers are known to be severely diminished in healthy aged individuals. A severe decline of switched memory B cells is also observed in normal ageing.[4] These latter cells can readily differentiate into plasmablasts after stimulation by the specific antigen and produce a robust humoral response.[5] Chronic HD results in B cell lymphopenia and alterations in B-cell phenotype that resemble normal ageing. This may act as an additional factor to relative immune deficiency of patients on dialysis. ■

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Alternating Episodes of True Hyperkalaemia and Pseudohyperkalaemia in Adult Sickle Cell Disease: A Nephrologist's Dilemma

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Keywords: Hyperkalaemia, plasma, pseudohyperkalaemia, serum, sickle cell disease, sickle cell nephropathy, thrombocytosis, true hyperkalaemia.

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INTRODUCTION

Sickle cell disease (SCD) predisposes the patient to recurrent episodes of acute painful haemolytic crisis. Sickle cell nephropathy is not uncommon in adult patients, and renal manifestations of sickle cell nephropathy include renal ischaemia, microinfarcts, renal papillary necrosis, and renal tubular abnormalities with variable clinical presentations.[1-4] Intravascular haemolysis and reduced glomerular filtration rate with renal tubular dysfunction predispose to true hyperkalemia.[3,4] Haemolytic crisis can be complicated by sepsis, leading to significant degrees of thrombocytosis, and thrombocytosis is a well-defined cause of pseudohyperkalaemia.[2] The authors have described a 40-year-old African American male patient with sickle cell

anaemia who exhibited alternating episodes of true hyperkalaemia and pseudohyperkalaemia, during the same hospitalisation.[5] Clearly, true hyperkalaemia is a potentially lethal condition. Simultaneously, the institution of inappropriate and intensive treatment of pseudohyperkalaemia leading to severe hypokalaemia is also potentially lethal.[6] The need for this caution is most imperative with the recent introduction of the safer, more potent potassium binders, patiromer and sodium zirconium cyclosilicate (SZC).[7]

METHODS AND CASE REPORT

The authors described a 40-year-old African American male patient with sickle cell anaemia who exhibited alternating episodes of true hyperkalaemia and pseudo-hyperkalaemia during a single hospital admission.[5] Admission true hyperkalaemia was accompanied by haemolytic crisis, sepsis, high anion gap metabolic acidosis (serum bicarbonate <5 mmol/L), and acute kidney injury. About 2 weeks into the admission, with normalised kidney function, he had demonstrated persistently elevated serum potassium levels, which persisted despite the addition of diuretics and daily SZC. An incidental normal ECG, despite a measured serum potassium of 6.7 mmol/L, led to the consideration of pseudohyperkalaemia. Simultaneous plasma potassium returned to be much lower than serum potassium, thus confirming pseudohyperkalaemia. The pseudohyperkalaemia was ascribed to severe thrombocytosis complicating sepsis (Figure 1). Subsequently, SZC was discontinued and the patient was soon discharged home without any further complications.

DISCUSSION

Pseudohyperkalaemia, first reported in 1955 by Hartmann and Mellinkoff,[8] is a marked elevation of serum potassium in the absence of clinical evidence of electrolyte imbalance. Simultaneous serum potassium exceeds plasma potassium by >0.4 mmol/L.[9] Pseudohyperkalaemia has mostly been associated with moderate to severe thrombocytosis or leukocytosis.[10]

Figure 1: Simultaneous trajectories of serum potassium, serum creatinine, and platelet count during the hospital admission.

Unmistakably, true hyperkalaemia is potentially lethal. Nevertheless, inappropriate treatment of pseudohyperkalaemia leading to severe hypokalemia is also life-threatening.[6] The authors believe that this is the first report of adult SCD demonstrating alternating cycles of true hyperkalaemia and pseudohyperkalaemia at different times during the same hospitalisation. It is imperative to draw attention to the new potassium binders, patiromer and SZC.[5] The authors advocate caution in the use of these potent potassium binders and to always give consideration to the presence of pseudohyperkalaemia under appropriate clinical scenarios. They posit that those providers treating patients with SCD must be aware of such a phenomenon to avoid the dangers of overtreatment of episodes of pseudohyperkalaemia.[5] One recurring mantra remains true most of the time: true hyperkalaemia in the absence of overt kidney dysfunction must always be viewed with circumspection and doubt. Iatrogenic, life-threatening hypokalaemia remains a real concern and must be avoided.[5] ■

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Congress Interviews

Robert John Unwin, Scientific Advisory Board member of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), and Peter J. Blankestijn, Council member of ERA-EDTA, spoke to EMJ about their respective roles within the society, their research interests and recent publications, and what the future of nephrology holds.

Featuring: Robert John Unwin and Peter J. Blankestijn.

Robert John Unwin

Professor Emeritus of Nephrology, former Professor of Nephrology and Physiology, University College London, UK; Scientific Advisory Board member of ERA-EDTA

Q1 What led you to pursue a career and specialise in the field of Nephrology?

A longish story. My early ambition in medicine was to be a surgeon, which I think is quite common among medical students, especially male, but I was greatly influenced by my university tutor, who was a neurosurgeon; although he had taken an unusual career path, which was the lesson for me. He had started out as a general physician or internist and then became a neurologist but was frustrated by what he saw as the limits of neurology; while he could make an elegant and often anatomically precise diagnosis, there was little he felt he could actually do for many of his patients and so he decided to train as a surgeon and become a neurosurgeon. He argued that there should be no set career path from A to B and that it should be possible to chop and change and move from A to C to D and then B, according to your interests and emerging talents. Very few medical students or young doctors at the start of their medical careers know exactly where their talents and interests lie in medicine, and they need the opportunity to sample and

to change course; this also has the advantage of providing some breadth in medical training by not being forced decide and specialise too early.

Back to me! After graduation, I came under the influence of an eminent Professor of Medicine in London at the time, who described himself as a 'para-nephrologist', meaning he was really an internist with an interest in nephrology, but more as physiologist than as a clinician interested in renal immunology or closely involved with kidney transplantation or dialysis. I began my experience of research with him exploring potential physiological and homeostatic links between the gastrointestinal tract and kidneys, and I was eventually sent to the USA to learn more in-depth renal physiology and the experimental technique of single nephron micropuncture. On returning to the UK, still not being trained yet as a 'card-carrying' nephrologist, I became for short time a clinical pharmacologist, which did not make a lot of sense with my interest and experience in renal physiology, so I decided to train, late in my career, as a nephrologist and was fortunate enough to be supported by a senior colleague in my 're-training'.

So, to answer your question, my interest in physiology and the central role of the kidneys as an organ system in controlling body homeostasis are really what led me into nephrology, and what for me became applied physiology in the care of my patients.

Q2 You currently have more than 600 publications to your name for your research in this field. What do you believe to be the current gaps in nephrological literature and what topics merit greater attention?

That seems a rather large number, but if you look at what I have published it is quite broad (a criticism perhaps), covering physiology, pharmacology, hypertension, and kidney stones; some of it original and much of it educational. What are the current gaps in nephrology? Well, the subject is so large and potentially all-encompassing that it is difficult to say with any certainty and there is an inevitable bias; progress is being made on so many fronts. However, I think an important challenge lies in making sense of 'big data'. Data collection and sophisticated analytical methods, including in data science itself, have almost out-stripped our capacity to make sense of it all, even with the advent of artificial intelligence.

"Our capability to make new findings and identify novel and often unexpected associations has leapt ahead of our ability to synthesise, hypothesise, and test, and to apply this newly acquired knowledge to treating patients, which is, of course, the ultimate goal."

Our capability to make new findings and identify novel and often unexpected associations has leapt ahead of our ability to synthesise, hypothesise, and test, and to apply this newly acquired knowledge to treating patients, which is, of course, the ultimate goal. For example, the major cardio-renal benefit and therapeutic advance from the new class of SGLT2 inhibitors was not anticipated from what was known of its target, a renal glucose transporter, and is still something of a mystery, but has emphasised the importance of a more holistic approach to patient care and management, the part played by serendipity, relying as it does on clinical observation, and the reality of multi-morbidity in our patients. I think we urgently need more (to restore) experimental medicine in human subjects, including patients, to properly assess (prioritise) and understand many of the exciting new findings emerging from basic science, and the analysis of the many large and increasingly available datasets. We have moved away from candidate-based testing of a mechanistic hypothesis to more unbiased data gathering and analysis (necessary 'fishing' in my view), but now we need to get back to generating more testable hypotheses, ideally in human subjects much sooner, when safe, than later. In my opinion, physiology and function are still the foundations and should be kept in mind during each future step forward.

Q3 You have been a Scientific Advisory Board member of ERA-EDTA since 2016, could you please explain what this position entails and how it contributes to the success of ERA-EDTA society?

"Patients benefit from the updates and educational support provided during the congress, as well as the sense of community given to nephrologists."

The Scientific Advisory Board has an increasingly important function in actively supporting and advising the ERA-EDTA Council in deciding its various scientific awards that recognise the important clinical or research contribution of individuals; its fellowship schemes that provide young nephrologists with the opportunity to work, carry out research, and train in nephrology centres outside their own country, and to help further their career; as well as the ERA-EDTA's own scientific initiatives through its various designated ERA-EDTA Working Groups; and, of course, guidance on the scientific programme for the annual ERA-EDTA meeting. It is a real privilege to be a current member of the Scientific Advisory Board.

Q4 The ERA-EDTA's mission is: "the advancement of medical science by promoting fundamental and clinical advances in the field of nephrology, dialysis, renal transplantation, hypertension, and related subjects." How much of an impact do you believe the ERA-EDTA congress has, both directly on nephrologists and indirectly on patients?

The ERA-EDTA has several key functions that I believe provide real benefit to its members and ultimately to patients. The regular newsletter and affiliated journals help publicise smaller sub-specialty meetings and encourage reporting and publication of original work from members and others in allied fields of medicine and surgery. The annual congress brings together nephrologists throughout Europe, but also more widely, and has become a growing international body that stands alongside the American Society of Nephrology (ASN) and International Society of Nephrology (ISN) meetings. Founded initially as a clinical society with a focus mainly on renal replacement therapies, dialysis, and transplantation, its scientific profile has risen significantly in recent years and its meetings are now more balanced between clinical and basic science, and it also provides essential educational courses and activities. The latter are very popular with delegates and are now a regular and integral part of the main congress. Patients benefit from the updates and educational support provided during the congress, as well as the sense of community given to nephrologists, especially those still in training and young investigators, and provides an opportunity for questions to be asked and for experiences to be shared.

Q5 This year's congress was held virtually. What do you believe to be the advantages and disadvantages of a virtual congress?

At first, I thought a virtual meeting would be much less appealing, because you cannot meet colleagues informally or by chance while, for example, moving between sessions or scheduling a chat over a coffee or a meal. However, I realised that while the loss of personal contact cannot be overcome, there are fewer distractions online; you do not lose time moving from one lecture hall to another, and you can rapidly hop between parallel sessions. The technology, apart from the odd glitch, has advanced so much that the speaker and panel members can be seen live, and the presentations are often easier to view than in a large lecture theatre or auditorium with the inevitable distraction of people entering and leaving. You cannot see fellow delegates, of course, but I think it is much easier for delegates to ask a question (type it) online and for the panel to quickly pick up on the questions to select and repeat (which itself is an advantage) and to spot a popular question. In an actual meeting, people are often shy and reluctant to ask questions, which are not always easy to hear or are sometimes not repeated, and the post-presentation discussion can often end up a little stilted. There is also the opportunity to compliment a speaker personally online, which is encouraging and no bad thing!

Finally, it means that everything can be (and now is) recorded and viewed again later. While not a substitute for a physical meeting, I think a virtual meeting held in parallel can widen accessibility for those who cannot attend in person, but who would still like to participate. As with 'home-working', I think this will be here to stay in some form.

Q6 You presented an insightful session in this year's congress titled: 'COVID-19 and history - a perspective from the great influenza pandemic of 1918'. What have been your personal experiences during the COVID-19 pandemic, and what lasting impacts do you predict the pandemic will have on the field of nephrology?

I have not had direct patient contact during the pandemic, but I have been able to work from home with regular online meetings as part of my current work in early drug discovery, including ideas to do with remote monitoring of patients, since most outpatient consultations have been by telephone or online, and I think this will continue in some form for both patient and doctor convenience, and to better manage limited clinical resources. Climate change was a theme of this year's congress and the smaller carbon footprint from less travel to and from hospitals and clinics is also an important factor.

I have had many discussions with younger colleagues who have been directly involved in patient care and it is clear that even when the pandemic is over, clinical practice will change and there will be fewer routine clinical visits to hospital; we are also yet to see the longer-term health consequences of the COVID-19 infection itself. However, the learnings for me from the 1918 flu pandemic, the subject of my talk, which although at a very different time to our own, were the importance of early and prolonged social distancing and that this could not be eased until, in the case of 1918 flu, there was a more controlled spread of infection that would not overwhelm the medical services available, and until 'herd immunity' could be achieved; today, for COVID-19, we have the vaccines to provide safer herd immunity, but we probably need at least 60% coverage of the population before we can lessen current restrictions. Closing schools was an important measure in 1918, as well as banning large public gatherings; quarantine at the time had limited impact and mask-wearing was thought to protect the wearer, rather than those he or she came into contact with. But an interesting finding from 1918 was that while the overall economic impact was significant, as it is now with COVID-19, it did recover quite quickly in the years that followed (until the Great Depression), and those towns and cities that enforced more prolonged social distancing had fewer job losses than those that did not; the argument that there is an either/or choice between health and the economy is misleading: health is the economy.

Q7 What are the most significant changes and innovations you have seen in the field of nephrology during your time working with the field?

As mentioned earlier, I think major advances have come from the creation and linking of clinical records and databases, and the establishment of large patient registries, as well as many national patient cohorts for study, and to set up biosample repositories (biobanks). While data protection is essential, I am always impressed by how willing many patients are to participate and to contribute to research, even when they will not benefit directly, at least in the short-term. All this activity has made it possible to analyse patient characteristics in some depth, including genetic factors, and to analyse for disease-related biomarkers using sophisticated analytical methods (proteomics, metabolomics, etc.).

Q8 You are currently working on research in diseases of the kidney and nephro-urology. Could you tell us the current stage that the research of this is in, and how it impacts patients diagnosed with kidney disease and other renal conditions?

I am no longer active in basic or clinical research as I was before. I still work with some former collaborators, but I am a step removed from designing or conducting research. In the last few years, I have been working in renal drug development with the pharmaceutical company AstraZeneca, which has given me the valuable opportunity to learn about, and better understand, what is needed to develop new therapies for kidney disease; the many challenges in basic science (confirming what has been published and making new discoveries) and the many difficulties and obstacles in transitioning a new drug for patient care into the clinic.

From my experience to date, I am a firm believer in a partnership between industry and academia, particularly in nephrology, as the best way of advancing and introducing novel and effective therapies for our patients; but we do need more clinical trials in nephrology, both smaller 'proof-of concept' trials and larger confirmatory and definitive trials. The generally slow progression of chronic kidney disease can make large studies costly and time-consuming, and some new thinking is required in trial design and implementation. COVID-19 may provide another learning for us in this respect, with the innovative RECOVERY trial design for sequential testing of drug treatments, and it might be something to explore and adapt for future trials in kidney disease.

Q9 What would your advice be to the younger generation who are following the same path and just beginning their career in this discipline. Where do you hope they will take the field of nephrology over the coming decades?

Be flexible and follow what interests you and what you are comfortable with, but always keep patients in mind; what you might do for them and what you can learn from them – a truism, I know, but every patient's story is different and always a rich source of the unusual or unexpected. We do learn from, and tend to remember, our patients.

Nephrology is perhaps the last bastion of general or internal medicine, because chronic kidney disease is either associated with or impacts almost every other organ system, and its management requires a broad and fairly comprehensive understanding of most other medical specialties. This makes nephrology an intellectually very attractive and stimulating discipline to take up and is attracting some of our best minds and most talented young physicians and research investigators. However, it is disappointing that so far, no drug has reached the clinic intended for the treatment of kidney disease from the outset; most of the current treatments used in nephrology have been adopted and adapted, apart perhaps from erythropoietin to treat anaemia.

I hope the next generation of renal scientists and nephrologists will help identify and test drug targets that cannot only slow kidney disease progression, but can also halt or even reverse it. Renal cell biology is revealing new opportunities for cell-based therapies and tissue regeneration, and the future is exciting with so much that is new for us to understand, to explore, and to contextualise. ■

Peter J. Blankestijn

Department of Nephrology and Hypertension, University Medical Centre Utrecht, Netherlands, 2021 Scientific Committee member and former Council member of European Renal Association – European Dialysis and Transplant Association (ERA-EDTA).

Q1 With over 30 years' experience in the nephrology field, what initially inspired you to pursue your career in this discipline? What has motivated you to stay in the field?

During the time that I was carrying out my medical training in internal medicine there was no official nephrology subspecialisation. However, the internal medicine department, that I was working as part of my training, specialised in high blood pressure and nephrology. I quite enjoyed this sector and found it interesting. Following my training in 1991 I joined the department of nephrology and hypertension at the University Medical Center Utrecht, Netherlands. It was more accidental at that time; however, I am perfectly happy with the choice as it is an interesting discipline. Working in a university medical centre setting involves three different aspects: education aspect, patient care, and research, and this combination is very broad. My passion and ideas are involved in the three major fields and that is where I thrive. So to say, I prefer to work in a university setting compared to a large community hospital and this has motivated me to remain this field.

Q2 You are a scientific committee member of ERA-EDTA, what inspired you to join, and what have been your proudest achievements?

I have been an active member of the ERA-EDTA society for 15 years perhaps a bit longer. I have been member of several committees and boards. Over the past couple of years, I have been working on the sustainability. The European Commission has identified the transition to a more sustainable society as one of its main objectives and has defined very ambitious targets. This ambition needs to be translated into the healthcare sector as well, which is quite a big task, because the healthcare sector is particularly polluting to the environment. The sustainability agenda started a couple of years ago and is now becoming increasingly clear that it is an important issue. I am happy that at least I can say that I have been able to increase awareness in the society on this subject. However, we are only at the beginning and still much needs to be done.

Q3 What is one of the biggest challenges for the ERA-EDTA in their goal to promote the highest standard of practices in nephrology in order to benefit patients?

I think the biggest challenge within the nephrology society is to have healthcare professionals ensuring that patients have access to proper care. In most western countries this is not really an issue but in other parts of the world this is a major issue. Therefore, trying to find ways where we, as a society, could play a role in achieving this. The second challenge is highlighting how climate change and pollution have tremendous effects on health, including the kidneys. We, as a society, are learning and adapting to finding ways to handle this crisis. We need to find ways to a more sustainable environment, and this is a real big task for healthcare community in general. The solution is first realising that this is the case and then finding ways to counteract these negative effects. Obviously, we need to try and mitigate our own contribution to climate change

"We are only on square one, the mission of the ERA-EDTA in regard to climate is ambitious as we would like to achieve 55% reduction of carbon footprint of the society by 2030, similar to the ambitions of the European Commission

and pollution. We are only on square one, the mission of the ERA-EDTA in regard to climate is ambitious as we would like to achieve 55% reduction of carbon footprint of the society by 2030, similar to the ambitions of the European Commission. England is ahead of us in this aspect. The sustainable development goals are already on the agenda of the National Health Service (NHS) for quite some years now and is an excellent example on how to deal with this. This is on our agenda for the coming 5–10 years in order to make a real change.

Q4 You are chairing quite a few sessions in ERA-EDTA congress 2021. Which sessions are you most looking forward to at ERA-EDTA 2021? Why?

What I find exciting are the late-breaking trials which included the latest research with expert presenters. This year there are few sessions in the programme dealing with this environmental issue and the health sustainability subject. Last year was the first time we had specific sessions on this subject. However, we decided to cover these topics more extensively in ERA-EDTA 2021. I also have a presentation on introducing the sustainable development goals of the United Nations (UN) into clinical practice. Additionally, I have a presentation on patient-reported outcome, how to incorporate that in everyday clinical practice.

Q5 Early observations of coronavirus disease have shown that the virus can cause kidney injury, albuminuria, and elevated creatinine levels. What have been your personal clinical experiences during the COVID-19 pandemic, and what lasting impacts do you predict the pandemic will have on the field of nephrology?

Interesting question. Well, nephrologists are not typically in the first line of defence. These are mainly doctors working in the emergency and intensive care unit, especially within the infectious disease department. Occasionally nephrologists are involved in severe cases. Kidney damage can occur quite seriously in some patients and in these instances, nephrologists are able to offer their services. The other type of nephrological expertise involvement in COVID-19 is with patients with a kidney transplantation and

those undergoing dialysis. Both groups consist of high-risk patients, and we have seen quite a few cases where COVID-19 is fatal, due to serious pulmonary and renal complications.

Q6 You recently co-authored in a paper titled, "funding kidney research as a public health priority challenges and opportunities".[1] What were the main takeaway points from this paper? What areas of kidney research do you believe merit wider attention?

Prevention should be one of the main approaches, aiming to delay the process of kidney function deterioration. In a way one might say that as a public health system may have failed, because the main task should be to keep patients with kidney failure away from the need of dialysis or kidney transplantation. A big emphasis on this paper was that prevention from a patient perspective should be key. Treatments are expensive, I think we all agree that prevention is basically beneficial for both the patient and the healthcare and societal sector.

Q7 You also co-authored a paper titled, "Nephrology: achieving sustainability".[2] Please share with our readers more information about this article?

This was a short, editorial article accompanying another paper whereby a substantial number of dialysis centres in France, reported on their measurements of environmental impact. This was the first extensive paper reporting on a large number of treatments to give an idea of what the environmental impact of dialysis means. The authors also described how you can modulate or reduce this effect. In the editorial we discussed what the dialysis centre itself, the manufacturer and suppliers of materials can do to reduce environmental impact. It's informative in this respect, as it is setting the stage for further steps to be taken.

Q8 Your research focus has been on chronic kidney disease, hypertension, and haemodialysis. Are there any innovations on the horizon in this research area that you think are particularly noteworthy?

With respect to dialysis, I mentioned earlier that the real emphasis should be on prevention however once patients are on dialysis, we need to deliver the best possible care. My colleagues and I are working alongside in a large European trial comparing two types of therapies, that is standard haemodialysis versus online haemodiafiltration. Our hypothesis is that hemodiafiltration offers advantages over the present-day standard. If that turns out to be case, then it could mean a real improvement and progress in the field. We will also report on the patient reported outcomes. Any improvement in these outcomes, could be very meaningful as well.

Q9 Lastly, what advice would you give to young, aspiring nephrologists?

This really an interesting field whereby a lot of developments are needed. Clear questions are on the table, therefore my advice to young nephrologist is to become active in trying to modulate, or better: take part in making the future. ERA-EDTA society has an active young nephrologist group, this is really encouraging to see. This young generation of nephrologists are curious and eager to learn. They want to share ideas with us and discuss what should be on the agenda for the future generations. They ask the right questions on how to get organised and tackle the current issues in the best possible way. Sharing information and ideas within the field is the best way to achieve success. So my advice would be, to be active in and play a part in making the future developments in the field of nephrology. ■

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Interviews

Kenar D. Jhaveri spoke to EMJ about his ongoing passion for nephrology, current research and innovation within the discipline, and highlights on COVID-19-related acute kidney disease.

Featuring: Kenar D. Jhaveri

Kenar D. Jhaveri

Professor of Medicine and Associate Chief in the Division of Kidney Diseases and Hypertension, Hofstra/Northwell School of Medicine, Hempstead, New York, USA

Q1 What inspired you to pursue a career in nephrology?

When I was training, nephrologists were regarded as the 'detectives' of medicine. Growing up, I really enjoyed reading and watching detective stories. Nephrology allowed for a good blend of excellent medicine and the use of my diagnostics skills to become a good detective. In addition, during medical school and residency, several key mentors made nephrology the field I would ultimately choose. Nephrology allows for a great balance of primary care and specialised medicine. It has something for everyone: acid–base for math lovers; glomerular diseases and transplant for the immunologists; critical care and cardio-nephrology for the fast-paced, procedural-based minds; dialysis and chronic kidney disease care for those who want to improve quality care; the list goes on. Nephrologists are super-internists.

Q2 What sparked your interest in glomerular diseases?

Glomerular diseases have a special place in the heart of the nephrologists. To me, glomerular diseases are an enigma and likely one of the most mysterious diseases of the human body. Podocytes are fascinating cells. I enjoy taking care of rare diseases and diseases that affect the immune system; hence, glomerular diseases are a passion of mine. In addition, there is no 'cookbook' for the treatment of glomerular diseases; rather, [care is] very individualised. Research in this area of nephrology is quickly furnishing and more therapeutics are on the way. Targeted therapies to treat certain glomerular diseases are likely to be just around the corner.

Q3

What was the key message of the book you co-authored, 'Onconephrology', which covers pathophysiology and management of kidney diseases in patients with cancer, that you were trying to deliver? And have you seen improvement in treatment over the last few years?

Onconephrology is a field of nephrology that encompasses the complex interplay of cancer and the kidney. The fields of haematology and oncology have been on an exponential rise. The rapid development of therapeutics in oncology has led to the use of novel agents to treat cancer. The kidney is an organ directly affected by cancer and the effects of cancer, but it is also an organ that can be a target of the side effects from many cancer therapeutics. The book that was released in 2013 was one of the earlier books in this field to highlight the important message to nephrologists about this novel subspeciality in nephrology. The nephrologist that deals with patients with active cancers such as myeloma, amyloidosis, lymphoma, renal cell, and others, now has to become familiar with several developing side effects of novel therapies in this field. In the last 4 years, we have seen several advances in this field. There are now many centres of excellence around the USA, more interest in subspecialising in this area of nephrology, more original investigations looking at different topics in onconephrology, and increased awareness among haematologists and oncologists. Over the last 4 years, the American Society of Nephrology (ASN) also has an abstract submission category for Onconephrology. The field has clearly evolved in the last 9 years.

"For researchers, this field is ripe for action; with an increasing number of research opportunities in glomerular diseases, dialysis modalities, and AKI, the future is really bright."

Q4

Having ran a successful teaching-oriented blog titled 'NephronPower', what would you say is the mission behind its creation and where can we expect to see your focus lie in the coming years?

When I was in my first year of practice in 2009, I was inspired by a blog called The Renal Fellow Network, founded by the late Nate Hellman. I felt as an educator that blog writing would promote education through a different form. Hence, I started this teaching blog to educate trainees or whoever wanted to learn via short summary posts of various topics. For me, it was my knowledge diary. Every time I learnt something new, my blog would have a post on it. 'Teach as you learn' is my motto. Share the knowledge! Over the last decade, the blog has evolved from simple posts to quizzes, concept maps, and other ways of knowledge sharing. My mission is simple: knowledge sharing should be easy, succinct, and done through various forms (prose and pictures). We need to reach various genres of learners and various forms of learners. The blog hopefully does that. I plan to continue evolving the blog as the times and learners change. Concept maps and quizzes are my favourite posts to do on the blog.

Q5

You have recently been appointed as the Editor in Chief for the American Society of Nephrology (ASN) Kidney News. Could you please explain what this position entails? What has been your proudest achievement in this position?

I could not be more grateful for this honour bestowed on me by ASN. A diverse editorial board consisting of experts from all over the USA and the world really helps make the journal successful. Our goal is to highlight important nephrology issues and topics in a timely manner. We also want to use this platform to promote the field of nephrology to junior trainees and excite them about this amazing field. Since I just started the role in January 2021 what I am most proud of is the entire editorial board team: they are energetic, powerful, diverse, and dedicated.

Q6

As a nephrologist, how do you think the COVID-19 pandemic has affected the advancements in your field? What advice would you give to healthcare practitioners in the same field?

I think that nephrologists around the world were on the front line during the pandemic. Due to the fact that 10–40% of patients admitted with COVID-19 get acute kidney injury (AKI), the care from nephrologists was crucial in the pandemic and it is still ongoing. In addition, managing COVID-19 in the dialysis unit, in transplantation, and now the vaccine response in patients with dialysis and transplants is an important part for nephrologists. The field of AKI and immunology has advanced due to the COVID-19-related AKI, in my opinion. This also allowed for the increased collaboration of nephrologists and other medical specialities to come together for the science and to learn about COVID-19-related AKI. While non-COVID-19-related research stopped for some time during the pandemic, the field of nephrology has produced some amazing new discoveries. Some examples of these are membranous nephropathy antigen developments, novel therapies for lupus nephritis and anti-neutrophil cytoplasmic autoantibody vasculitis, and ongoing novel therapies for anaemia using hypoxia-inducible factor stabilisers, to name a few. All of these developments were published during the pandemic. I think that the COVID-19 pandemic is teaching us few things: collaboration brings out the best in us and collaboration helps our patients. The pandemic has also taught us that virtual platforms can be utilised to improve our work-life balance and still allow for advancements in nephrology.

Q7 Having recently published a paper and presented on the topic of hypercalcaemia and its association with immune checkpoint inhibitors, could you give some insight into this novel topic? What do you believe are the current gaps in the literature and what topics merit greater attention?

Immune checkpoint inhibitors (ICI) are revolutionising care in patients with cancer. AKI has been reported with an incidence of 2–4% in acute interstitial nephritis. In addition to acute interstitial nephritis from ICI therapy, we are noticing additional glomerular pathology along with a series of electrolyte disorders. Hyponatraemia is common, most likely being due to syndrome of inappropriate antidiuretic hormone secretion. What is interesting, however, is that endocrine side effects of ICI lead to both hyponatraemia and hypercalcaemia. Hypercalcaemia in ICI therapy can be due to multiple mechanisms: from endocrine causes such as adrenalitis (primary or secondary) and thyroid disorders to rare sarcoidosis-like reactions and parathyroid hormone-related protein production as a result of ICI therapy. In addition, in many cases there is an entity called pseudo-progression of tumour, which leads to hypercalcaemia. This topic really highlighted to me the unknowns of our immune system. ICI therapies are showing us what the literature has not seen before. Mechanisms of the ICI therapy that I use trigger a parathyroid hormone-related protein production, which needs further study. Why some patients develop sarcoid-like reactions and others adrenalitis is also an area that needs to be studied.

"I think that the COVID-19 pandemic is teaching us few things: collaboration brings out the best in us and collaboration helps our patients."

Q8 What advice would you give to aspiring nephrologists?

Nephrology is a fun and exciting field. From dialysis, immunology, transplant, glomerular diseases, acid–base, critical care, AKI, to hypertension, nephrology offers a variety of choices for anyone who loves general internal medicine. It has a fine balance of inpatient, outpatient, and dialysis care. It allows for an excellent work–life balance. For researchers, this field is ripe for action; with an increasing number of research opportunities in glomerular diseases, dialysis modalities, and AKI, the future is really bright. What I usually tell aspiring medical students and residents is: do not go after financial security or lifestyle. Do what you are passionate about and the rest will eventually fall into place.

Blood Volume Monitoring: A Clinical Tool to Guide Ultrafiltration in Volume Control and Optimisation of Intradialytic Blood Pressure

EDITOR'S PICK

The relevance of blood volume monitoring in patients on dialysis is that the overload is responsible for poorly controlled hypertension, increased cardiovascular events, and increase all-cause mortality. Finding a real-time calculator located on the arterial blood line could prove a great help both to guide ultrafiltration, assure dry weight, and prevent intradialytic hypotension events.

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Abstract

The importance of extracellular volume control and avoidance of volume overload has been well documented in relation to the management of patients with chronic haemodialysis. Chronic volume overload results in poorly controlled hypertension, increased cardiovascular events, and increased all-cause mortality. Traditional methods of dry weight assessment have relied on clinical assessment to guide volume status. The challenge of achieving the balance between dry weights and preventing intradialytic complications is a formidable one. In order to achieve this, reproducible and sensitive methods are desirable to aid objective quantification of volume status. One such method is by the use of blood volume monitoring, which is achieved by real-time calculation of changes in relative blood volume via a cuvette placed in the arterial blood-line, which can be used to guide ultrafiltration targets during the haemodialysis session. This review article examines the use of blood volume monitoring as a tool to guide ultrafiltration during dialysis and to examine the current evidence to supports its use in assessing dry weight and in preventing intradialytic hypotension events.

INTRODUCTION

The importance of extracellular volume control and avoidance of volume overload have been well documented in relation to management of patients with chronic haemodialysis. Chronic volume overload results in poorly controlled hypertension, increased cardiovascular events, and all-cause mortality.[1-3] Traditional methods of dry weight assessment have relied on clinical assessment to guide volume status. Unfortunately, relying on clinical signs of volume overload and assessment of dry weight correlates poorly with a true euvolemic state. Various studies have shown that up to 25% of patients in haemodialysis cohorts are chronically volume overloaded.[4,5] Indeed, according to Agarwal et al.,[6] markers of intravascular volume expansion, such as inferior vena cava diameter, blood volume monitoring (BVM), inflammatory markers, and plasma volume markers, may not be directly reflected by the clinical finding of oedema.[7]

The achievement of dry weight is associated with improvement in blood pressure control[8-10] and reduction in the requirement for antihypertensive medication.[5] Blood pressure control without the use of pharmacotherapy is a strong predictor of survival in the population on dialysis and hence dry weight achievement, by extension, is a positive prognostic factor.[11] Conversely, aggressive ultrafiltration and targeting an inappropriately low dry weight can lead to intradialytic hypotension (IDH), nausea, central nervous system dysfunction, cramping, and risks compromising vascular access and worsening residual renal function.[6,12]

The challenge of achieving the balance between dry weight and preventing intradialytic complications is a formidable one. In order to achieve this, reproducible and sensitive methods are desirable and would aid quantification of volume status. One such method is the use of BVM, which is achieved by real-time calculation of changes to relative blood volume via a cuvette placed in the arterial bloodline. These calculations can then be used to guide ultrafiltration targets during haemodialysis sessions.[4,13,15] This review article examines the use of BVM as a tool to guide ultrafiltration during dialysis and examines the current evidence to support its use in assessing dry weight and in preventing IDH events.

BLOOD VOLUME MONITORING IN PRACTICE

The use of BVM dates back to the early 1990s when CRIT-LINE® technology (Fresenius Medical Care, Bad Homburg, Germany) was first used as a non-invasive method of measuring haematocrit changes during haemodialysis, in real time, by connection of an additional monitor to the dialysis arterial line set-up.[16] This technology has continued to evolve, with some haemodialysis platforms now including software that uses continuous BVM biofeedback to automatically optimise ultrafiltration during the treatment (HemoControl®on the Artis Pysio® system, Baxter, Deerfield, Illinois, USA). While the mechanism of each BVM system may differ slightly, the underlying fundamentals are similar. As ultrafiltration removes fluid from the intravascular space, it changes the haematocrit, concentration of protein, and overall density of the blood.[17,18] Changes in the density of the blood can be determined by the velocity at which sound travels from the ultrasonic transmitter to the receiver; from this the relative blood volume (RBV) can be calculated within 2.9% accuracy.[18-20] A flat BVM curve during a dialysis session suggests that the plasma refill rate is occurring at an equivalent or higher rate than ultrafiltration (UF). Hence, a flat curve signals that there is scope to further increase the UF target and adjust the dry weight of the patient in the right clinical setting. A 'flat-curve' has been defined as a <5% reduction in RBV during the course of treatment. For patients with a >5% drop in RBV, a plasma refill test can be conducted at the end of the dialysis session. This is performed by turning off UF and rechecking the RBV after ten minutes; a vascular refill resulting in a ≥1.5% increase in RBV is consistent with excessive refill from extravascular compartments, thus indicating volume overload.[12] Patients with a >5% drop in RBV and a plasma refill of <1.5% are considered to have adequate UF and accurate dry weight goals.[12,21-24] (Figure 1). An RBV critical level is also determined to guide the rate of UF and in theory prevent IDH events. RBV critical levels are calculated by documenting the RBV level at which a patient develops symptomatic hypotension.[25] While BVM is useful in most patients on dialysis, one of the main limitations is its unreliability in patients with low UF rates (<2.5 mL/kg/hour).[21]

BLOOD VOLUME MONITORING AND DRY WEIGHT

The concept of dry weight dates nearly as far back as the invention of intermittent haemodialysis.[7] The definitions of dry weight have changed over time but can be defined as the lowest post-dialysis weight tolerated without significant signs of hypovolaemia.[6,16,17] The DRIP trial[26] found that extracellular volume expansion may be present even in the absence of clinical signs. This supports the clinical practice of dry weight challenging as a first-line strategy to improve blood pressure control as extracellular expansion is often accompanied by hypertension. Studies have quoted the prevalence of volume overload in patients on dialysis to be as high as 25%, demonstrating the clinical burden it poses on dialysis management.[4,5,27]

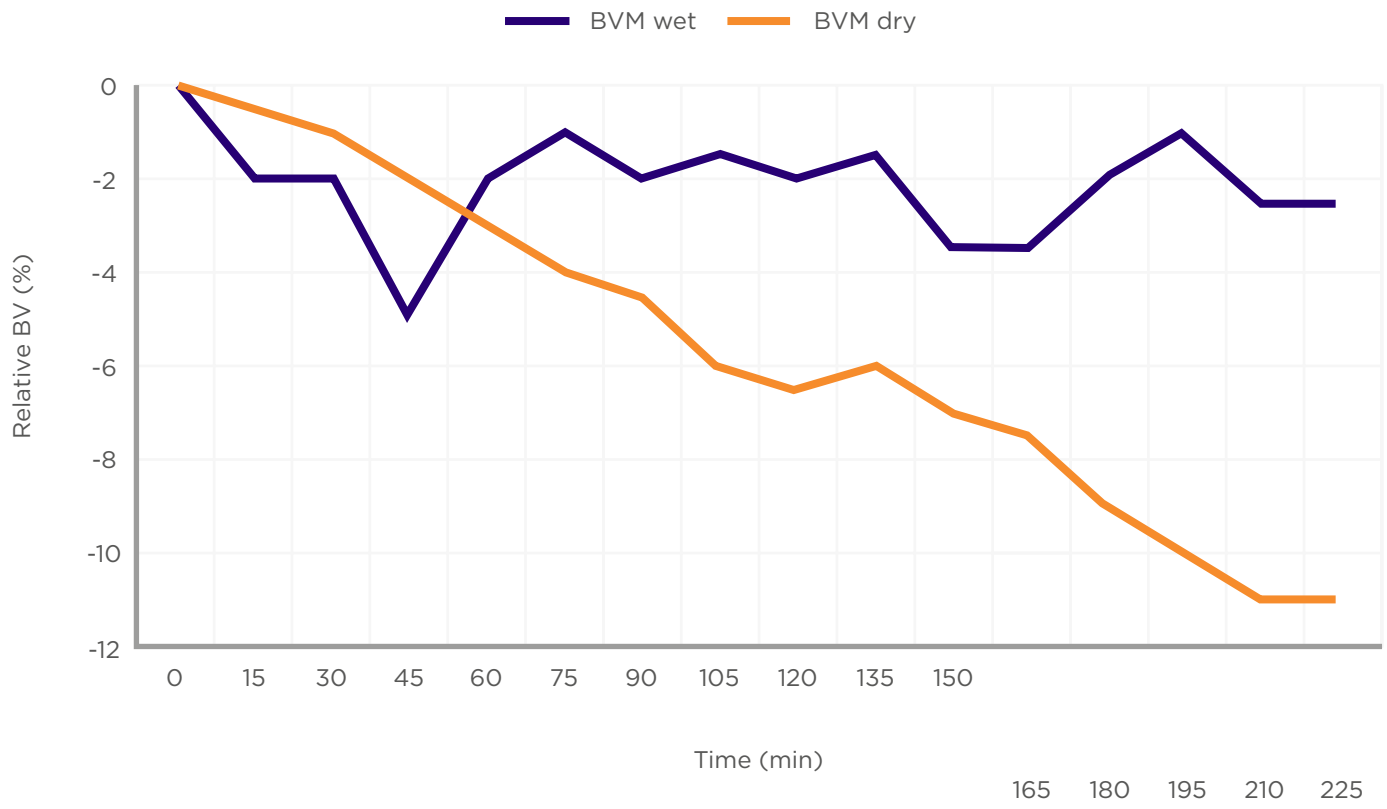

Figure 1: Comparison of blood volume monitoring wet versus blood volume monitoring dry.

A relative blood volume reduction of >5% and <1.5% relative blood volume plasma refill at the end of ultrafiltration treatment are classified as blood volume monitoring dry.

BVM: blood volume monitoring.

Table 1: Comparison of trial outcomes in utilisation of blood volume monitoring-guided ultrafiltration goals.

Publication	Study type	Study design	Population	Outcome
Hecking et al.,[23] 2012	Multicentre RCT	4-week, multicentre RCT using BVM guidance for dry weight reduction in fluid-overloaded patients on HD defined as ECV >15% Triple-arm analysis 1:1:1 comparing UCR-guided HD versus UTR-guided HD versus HD CONV	64 patients (22 CONV, 20 UTR, 22 UCR) Male: 60% Female: 40% Mean age: 62 years	Significantly lower IDH complications in UTR (21±21%) versus UCR (39±27%) versus CONV (34±20%) Overall SBP reduction 17±22 mmHg, with no significant difference between groups
Rodriguez et al.,[22] 2005	Single-arm, Phase 3 prospective study	Phase 3 prospective study of 28 stable patients on HD using Crit Line III monitors to assess DW Phase 1: time dependence of vascular refill after HD completion Phase 2: intradialytic changes in blood volume and post-dialytic vascular compartment refill when UF stopped for last 10 minutes of HD Phase 3: evaluation of DW changes from using BVM versus estimated DW previously	28 Patients Male: 75% Female: 25% Mean age: 68 years	67.9% of patients had their DW decreased 46.4% had DW reduced by >1 kg 32.1% had their DW increased DW pre-study were estimated by a dialysis medical director and nephrology nurse. DW was defined as lowest weight that a patient could tolerate without signs/symptoms of hypovolaemia
Hussein et al.,[12] 2016	Randomised cross-sectional observational study	Randomised cross-sectional observational study of 169 patients on HD across five centres, using BVM on a single session to estimate DW compared to clinician-assigned DW	169 patients Male: 58% Female: 42% Mean age: 64 years	73/169 patients (43%) were volume-overloaded based on BVM curve 54/169 (31.9 %) were BVM wet despite reaching target DW based on clinical assessment BVM wet was defined as failure of RBV to drop by 5% or vascular refill >1.5% at end of HD session

Table 1 continued.

Publication	Study type	Study design	Population	Outcome
Maduell et al.,[21] 2013	Observational cross-sectional study	Observational cross-sectional study of 55 patients on HD, followed for 7 HD sessions, to determine sensitivity of BVM in fluid status assessment	55 patients Male: 67% Female: 33% Mean age: 63 years	Using receiver-operating characteristics analysis, BVM had moderate sensitivity in detecting FO between 1–3 L (AUC: 0.60-0.65), slightly higher sensitivity for FO <1L (AUC: 0.7), and was most sensitive at detecting FO >3L (AUC: 0.85) Volume markers used were 1) Slope4h defined as the linear slope of the RBV decrease over the whole treatment; 2) RBV % reached at end of treatment; and 3) volume index defined as RBV slope over full treatment and normalised by UFR over post-weight

AUC: area under the curve; BVM: blood volume monitoring; CONV: conventional haemodialysis; DW: dry weight; ECV: extracellular volume; FO: fluid overload; HD: haemodialysis; IDH: intradialytic hypotension; RBV: relative blood volume; RCT: randomised controlled trial; SBP: systolic blood pressure; UCR: dialysate conductivity-regulated; UF: ultrafiltration; UFR: ultrafiltration rate; UTR: ultrafiltration- and temperature-regulated.

When the importance of volume control is discussed it is important not only to correlate it with adequate dialysis goals but also to examine the long-term consequences of a chronically fluid-overloaded state. Patients with end-stage kidney disease are unable to maintain fluid and salt haemostasis and hence volume overload plays a key role in increased cardiovascular events in the population on haemodialysis.[28-30] The intermittent nature of haemodialysis results in a constant flux between dry weight and intradialytic weight gain, which is associated with cyclical cardiac stress and ultimately cardiac remodelling.[31] The persistent hypertension resultant from chronic volume overload lends itself to the development of left ventricular hypertrophy.[32] Left ventricular hypertrophy causes both systolic and diastolic dysfunction, which predisposes patients to the risk of fatal arrhythmias.[28,33] It is unsurprising that cardiovascular disease accounts for over half of all-cause mortality in the population on dialysis given the above and accelerated vascular calcification.[34] Given the clinical significance of this issue, clinical research into developing strategies to aid judgement of appropriate dry weight is ongoing. One such strategy is investigating the effectiveness of BVM as a predictor of dry weight and appropriate goal-directed ultrafiltration.[5,12,14,21-24]

The data surrounding BVM as an effective tool in the management of ultrafiltration in patients on dialysis has yielded mixed results. The CLIMB trial[14] hypothesised the use of Crit-Line technology to monitor intradialytic haematocrit would decrease patient morbidity in comparison to conventional methods based on symptoms, blood pressure, weight, and physical exam. However, results from the trial found that there was a greater number of hospitalisations and mortality in the Crit-Line interventional arm than the conventional arm of the trial. The authors advised that the results of the trial should be interpreted with caution as there may have been a failure to randomise clinical variants among the two study groups equally. However, the trial casts doubt whether quantitative monitoring via a BVM is superior to clinical judgement.

Hecking et al.[23] described the use of BVM with regulation of ultrafiltration and dialysate conductivity (UCR) and/or regulation of ultrafiltration and temperature versus a conventional control group to decrease dry weight in fluid-overloaded patients on haemodialysis. The study attempted a rapid dry weight reduction in a volume-overloaded dialysis population. While the trial showed that there were fewer intradialytic complications in the ultrafiltration and temperature group (20±19%) versus UCR (47±27%) and the conventional group (41±30%), the overall complication rate remained high. Despite dealing with a population deemed volume overloaded, the rates of intradialytic hypotension mirrored that of the DRIP trial.[26] The authors noted technical mistakes in 36% of UCR dialysis sessions and therefore the trial results are to be interpreted with caution. A 17±22 mmHg reduction in systolic blood pressure was noted following dry weight reduction; however, there was no significant difference between each of the groups. This suggests that dry weight reduction results in improved blood pressure control regardless of the modality used. Similar findings in blood pressure were also demonstrated regarding dry weight reduction in the DRIP trial.[26]

BVM is unable to directly define dry weight since intradialytic changes in blood volume only account for the plasma compartment.[12,35] However, the extracellular compartment can mirror intradialytic changes reflected by the rate of vascular refilling.[22,36] Rodriguez et al.[22] hypothesised this in a study using Crit Line III monitors to assess dry weight. The trial theorised that intradialytic changes and post-dialytic refilling are both indirectly related to the composition of the extracellular compartment. Using Crit Line III monitors, all 28 patients in the trial had their dry weight adjusted from baseline assessment, 19 patients had their dry weight decreased, and nine patients had their dry weight increased. The changes to dry weight were based on post-dialytic vascular compartment refill and patient symptoms. The authors concluded that BVM, in conjunction with clinical assessment, was effective in achieving true dry weight. Similarly, Hussein et al.[12] found a high prevalence of volume overload in their study population. Forty-three percent of the 169 patients assessed were noted to be BVM wet, defined as failure to drop blood volume below -5% or an increase in blood volume by 1.5% during vascular refill. As such, dry weights were adjusted to new dry weight targets based on BVM findings. Maduell et al.[21] concluded from their study of 55 patients that BVM was effective in determining high levels of volume overload but was less useful in detecting low-to-moderate levels of fluid overload (Table 1).

Given the range of results found within the literature, it is clear that the theory behind BVM doesn't always correlate with findings in the patient population on dialysis. Achievement of dry weight can be hampered by intradialytic hypotensive episodes, which may not be solely related to intravascular volume status. Blood pressure changes during dialysis are multifactorial and include reduction in vascular tone and autonomic dysfunction, which are particularly important in the patient population who are on dialysis and diabetic.[37]

BVM AND INTRADIALYTIC BLOOD PRESSURE

Intradialytic blood pressure issues, predominantly intradialytic hypotensive events, are common among the population on dialysis with up to 30% of dialysis treatments complicated by intradialytic hypotensive events.[38] Intradialytic episodes are not only a source of morbidity for patients but also have a significant impact on the efficacy of dialysis sessions, ultrafiltration goals, and cardiac dysfunction, and may compromise vascular access.[39-41] The definition of intradialytic hypotension (IDH) is defined as ≥20 mmHg drop in systolic blood pressure accompanied by symptoms of hypoperfusion. Intradialytic hypotensive events have been associated with increased mortality, cerebral atrophy, myocardial stunning, ischaemic heart disease, and loss of residual renal function.[6,12,42-47] The pathophysiology of IDH is multifactorial and includes a combination of changes in blood volume, reduced cardiac function, and failure of compensatory vasoconstrictive responses. Certain patient factors are associated with higher risk of IDH including diabetes, patients who are elderly and on dialysis, patients requiring longer haemodialysis sessions, and patients prone to autonomic dysfunction. Given the significance of intradialytic hypotensive events, a modality that could lead to the prediction or prevention of an event would be of great clinical benefit.[49,50]

Booth et al.[13] conducted a study to assess the correlation between BVM and associated hypotensive invents in 72 patients on dialysis. While the results found that BVM correlated with changes in haematocrit, serum albumin, and extracellular fluid volume, the trends in BVM did not mirror intradialytic blood pressure. The data from this trial showed that there was no relationship between relative changes in BVM and intradialytic blood pressure. Similar results were also found by Leung et al.[4] who conducted a 22-week, multicentre, randomised cross-over trial in 35 patients receiving regular intermittent haemodialysis who had >30% of sessions complicated by symptomatic IDH.[4] Following a 4-week run-in period to allow standardised dry weight assessment, dialysis prescription review, and rationalisation of antihypertensive medications, patients were randomised into a control group (best clinical practice) or the intervention group (best clinical practice plus BVM). The BVM group adjusted for ultrafiltration rate but not dialysate sodium. The primary outcome of the trial was symptomatic IDH defined as ≥20 mmHg drop in systolic blood pressure from baseline accompanied by symptoms of IDH.

At the end of the trial period there was no difference in the incidence of IDH between the two groups.

Bégin et al.[25] carried out a small study with more positive results for the use of BVM in the prevention of hypotension during haemodialysis. Seven patients on chronic haemodialysis with frequent IDH (>30% of dialysis sessions complicated by IDH) participated in a cross-over trial alternating between six consecutive sessions with blood volume regulation versus six standard dialysis sessions, for a total of 36 sessions. A dialysis session was considered event-free if symptomatic blood volume contraction did not occur, no sudden hypotensive event occurred, therapeutic intervention was not required, and departure from the dialysis unit proceeded as scheduled. The results showed a 74% increase in event-free sessions with use of BVM (50.8% versus 29.2% of sessions). While the results of this study had a positive result with the use of BVM to prevent hypotensive events, limited conclusions can be drawn given the small population involved.

De'ziel et al.[51] studied hypertension control in a population on dialysis with ultrafiltration goals guided by BVM. The primary end-point was variation in baseline systolic, diastolic, and mean blood pressure from baseline to the end of the study. A secondary end-point was variation in baseline to the end of the study in the number of nursing interventions for IDH. This was a randomised controlled trial of 57 patients on chronic dialysis over a 6-month period. Patients were randomised to receive standard haemodialysis versus Hemocontrol® (HC) haemodialysis. Of the 44 patients who completed the trial (22 in each group), home blood pressure readings were available for 36 (19 in the standard haemodialysis group and 17 in the HC group). The trial showed a significant overall decrease in systolic blood pressure in both groups but no significant difference between the two groups (mean systolic blood pressure in the standard group decreased from 150.6 to 138.0 mmHg, and in the HC group systolic blood pressure reduced from 162.5 to 147.6 mmHg). However, on analysis of the secondary end-point, there was a significant reduction in the number of interventions required in the HC group versus the standard haemodialysis group. In addition, a quality-of-life questionnaire showed an improvement in the burden of kidney disease in the HC group while there was a deterioration in quality of life in the standard group. Overall, the literature presents mixed results for the use of BVM as a preventive measure for IDH. Further larger studies are needed to further assess its utility for this indication (Table 2).

CONCLUSION

The use of BVM in both guiding ultrafiltration and preventing intradialytic hypotensive episodes has varied results in the literature. Given the significant interplay of physiological processes involved in volume control and haemodynamic changes in the population on haemodialysis, BVM may play a useful role in improving the efficacy and safety of care in addition to clinical assessment of patients, which is known to have its own limitations. However, further larger and more definitive trials, coupled with ongoing developments in technology, are needed to provide advances in this area.

Table 2: Comparison of trial outcomes in blood volume monitoring utilisation in intradialytic hypotension prevention.

Publication	Study type	Study design	Population	Outcome
Booth et al.,[13] 2011	Prospective audit	Prospective audit comparing mid-week dialysis sessions using BVM-guided UF versus standard dialysis on other days	72 patients Male: 50% Female: 50% Mean age: 55 years	No significant difference in IDH with BVM-guided sessions versus standard therapy
Leung et al.,[4] 2014	Multicentre, randomised cross-over trial	22-week analysis, single-blind study in IDH-prone patients comparing BVM-guided UF versus standard treatment	35 patients Male: 83% Female: 17% Mean age: 67 years	No significant difference in IDH events between control group and interventional BVM group
Begin et al.,[25] 2002	Prospective cross-over trial	12-week prospective cross-over analysis using "AB AB AB" design in patients prone to IDH (i.e., alternating six standard HD sessions with six BVM-regulated sessions for a total of 36 sessions)	7 patients Male: 57% Mean age: 76 years	74% increase in event-free dialysis sessions with use of BVM-guided sessions versus standard HD sessions
De'ziel et al.,[51] 2007	RCT	6 month, prospective RCT to assess incidence of IDH events in BVM-guided HD sessions versus standard HD	57 patients (28 standard HD + 29 BVM HD) Male: 52% Female: 48% Mean age: 66 years	42.9% decrease in IDH events in BVM compared to 35.7% increase in IDH events in control group

BVM: blood volume monitoring; IDH: intradialytic hypotension; HD: haemodialysis; RCT: randomised controlled trial; UF: ultrafiltration.

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Trace Elements and Chronic Kidney Disease: A Cross-Sectional Study from Jamaica

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Abstract

Background: Several environmental studies have reported that low-level exposure to nephrotoxic elements increases the risk of chronic kidney disease (CKD). In developing countries, finite resources can limit epidemiological studies and environmental risk assessment; however, the unique soil profile in Jamaica has raised some concerns for the potential exposure to populations who are of high risk.

Method: This study investigated the potential for using trace element profiling in CKD, by analysing blood concentration levels of vanadium, chromium, iron, cobalt, copper, zinc, selenium, strontium (Sr), arsenic, barium, cadmium, mercury, and lead. Trace element analysis was conducted using inductively coupled plasma mass spectrometry.

Results: One hundred and fifty-eight individuals were included and were predominantly of African descent (98%) and their ages ranged from 21 to 90 years old. Three main correlation clusters were evident: firstly, vanadium, chromium, copper, silicon, and selenium, with mercury and barium more distantly related; secondly, lead, arsenic, nickel, and Sr; and thirdly, iron and zinc. Cadmium was an

outlier. Blood Sr was strongly associated with estimated glomerular filtration rate (r = -0.83; p<0.001) and strong linear progression models (r^2=0.96; p<0.001). Algorithmic models placed Sr as the highest-ranking trace element biomarker (area under the curve: 95.6%; p<0.001).

Discussion: The decline in kidney function may result in the retention of non-essential trace elements. Strong corresponding trends between kidney function and blood Sr concentration indicate biomarker potential for a trace element with a unique profile in patients with CKD. Other significant relationships may also be unveiled as CKD biomarkers as trace element profiling is explored in the region.

INTRODUCTION

The global epidemic of diabetes and hypertension continues to foster the rapid increase of chronic kidney disease (CKD), which has an estimated prevalence of 13.4% worldwide.[1] The Caribbean region situated between the Americas is as vulnerable to these disease trends as anywhere else. In Jamaica, which is the largest English-speaking Caribbean island, the prevalence of diabetes and hypertension is 30% and 35%, respectively.[2] At least 150,000 Jamaicans have been estimated to be living with some form of kidney disease, of which approximately 2,700 are cases of CKD.[3,4]

The island is unique in that it contains significantly high levels of cadmium (Cd) soil reservoirs, with the highest levels registered at 409 mg/kg. These levels are more than the world's mean soil measurements, which range from 0.005 to 2.900 mg/kg.[5] Environmental studies carried out by the International Centre of Environmental and Nuclear Science, Kingston, Jamaica, detailing the bioaccumulation in staple foods of the Jamaican diet such as sweet potatoes, ginger, and rice, demonstrate the potential exposure pathways for toxic element exposure.[6-8] Biopsy studies have revealed the deposition of toxic metals in the kidney and liver of cattle reared in those areas.[9] The purported link of Cd to kidney disease, as well as the resurgence of industrial mining in recent times, has spurred interest in trace element analysis and related chronic diseases on the island.

Since the discovery of aluminium-induced neurological and bone disease in patients receiving dialysis, trace elements have been studied in relation to kidney disease and therapy.[10,11] Other studies suggest an increased risk of CKD, hypertension, and diabetes by virtue of low-level chronic exposure to toxic metals.[12,13] However, few environmental studies have evaluated element trends and their relationship to CKD in black ethnic groups even in international studies, despite the disproportionate burden of CKD that has been highlighted in these populations.[14] In low-income countries, such an undertaking is of low priority due to lack of financial resources and/or relevant infrastructure.

Trace elements are ubiquitous entities and a fair number of non-essential xenobiotics gain entry into the body via a multitude of ways, including through groundwater (arsenic, strontium, silicon), inhalation of silica dust (silicon), gasoline (lead), cigarette smoke, and soil (cadmium) and food contamination (arsenic, mercury).[15] Ordinarily, inadvertent intake of non-essential trace elements is neutralised by excretory pathways, and nascent biomolecular mechanisms reduce the likelihood of protracted renal exposure. However, the reduction of renal clearance will likely lead to the progressive accumulation of these non-essential elements in patients with CKD.[16] Dietary restriction introduced for the management of CKD may further potentiate exposure to non-essential trace elements that are found in high concentrations in the recommended food groups.[17] The propensity for xenobiotic elements to interfere with cellular processes, inducing cytotoxic responses and causing localised tissue injury while supplanting essential elements and reducing reparatory function, can further exacerbate the metabolic milieu commonly associated with complications of CKD.[18,19] The aim of this study was to investigate the trace element profile for Jamaican patients with CKD.

MATERIALS AND METHODS

Ethical Statement

Approval was granted in 2016 from the Medical Ethics Committee of The University of the West

Indies, from the Ministry of Health, and from the relevant municipal health agencies. Procedures followed were in compliance with the Declaration of Helsinki 1975, as revised in 2013.

Population

A cross-sectional study was carried out between 2016 and 2019 in Jamaica. Patients with CKD from three major renal clinics in Kingston, St. Ann Parish, and Manchester Parish were recruited; the Kingston clinic receives intake of patients from the southeast region of the island, while the other two clinics receive intake from the northeast and southern regions, respectively. All attendees at the respective clinics were approached and given equal opportunity to participate in the study; however, patients who did not meet inclusion criteria requirements were immediately eliminated from the sample population. Sixty-eight patients with Stage 5 CKD on haemodialysis (CKD-HD) and 61 patients with CKD from Stage 1 to 4 gave prior informed consent to participate in the study and were interviewed. Subsequently, 29 volunteers who did not have CKD were recruited by convenience sampling and gave prior informed consent and were interviewed. Of the eligible candidates, 96 study participants submitted fasting venous blood samples for trace element analysis.

Selection Criteria and Outcomes

The estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration formula. CKD, according to Kidney Disease Increasing Global Outcomes (KDIGO) guidelines, is defined as kidney damage (structural or functional) for >3 months with a loss of glomerular function or an eGFR <60 mL/min/1.73 m^2 and/or the presence of albuminuria (>30 mg).[20] Patients were classified Stage 1–4 according to KDIGO guidelines. End-stage renal disease (ESRD)/CKD-HD Stage 5 represented in this study was classified as having an eGFR <15 mL/min/1.73 m^2 and receiving renal replacement therapy (haemodialysis; HD).[20,21]

A priori evaluation of the subjects without CKD was guided by the following criteria: 21 years of age and older; living in Jamaica for at least 6 months with no known history of irregular elemental exposure through occupation or association; and in good health (on declaration and confirmed by follow-up medical evaluation). Volunteers who reported heavy drinking, smoking, or heavy mineral supplementation were excluded from this cohort. Of the 29 self-declared non-CKD group, 24 participants were eligible and fell within the reference ranges for systolic and diastolic pressure and renal function indices.

Sample Collection and Handling

Special care was taken to avoid entry of external contaminants into the blood samples. Blood was extracted into trace-element-free tubes (K_2EDTA BD vacutainer, 4.0 mL). For patients with CKD-HD Stage 5, blood extraction was conducted pre- and post-HD. To reduce additive effects, antiseptic agents containing betadine and iodine derivatives were avoided during sample extraction. Powder-free sterile gloves and 70% isopropyl alcohol were used during sample extraction and handling. Specimens were stored at -80 °C until analysis. Serum samples were also withdrawn and submitted for routine biochemical analyses, including serum creatinine.

Sample Preparation and Elemental Analysis

All vials and tubes during sample processing were acid washed overnight with 1% nitric acid (HNO_3) and rinsed with deionised water. For acid digestion, trace metal grade concentrated HNO_3 was submitted to sub-boiling distillation to produce high-purity HNO_3. Element-free propylene tubes were used. 2.0 mL of HNO_3 was added to 0.1 mL of blood in a Teflon vial and digested overnight on a hotplate at 100 °C, evaporated to incipient dryness, and redissolved in 2% HNO_3. Samples were analysed by inductively coupled plasma mass spectrometry on an Agilent 8800 ICP-QQQ (Agilent, Santa Clara, California, USA) for iron (Fe), zinc (Zn), silicon (Si), vanadium (V), chromium (Cr), cobalt (Co), nickel (Ni), copper (Cu), arsenic (As), selenium (Se), strontium (Sr), Cd, barium (Ba), mercury (Hg), and lead (Pb). For ease of discussion, trace elements were grouped as essential and non-essential.

Clinical Evaluation

Demographic data and medical history were elicited by assisted interview. Physical examination was carried out by trained personnel to acquire anthropometric measurements and blood pressure (BP). Biochemical analysis was

also performed to establish renal function, and the eGFR was calculated using the CKD Epidemiology Collaboration formula.

Statistical Analysis

Statistical analysis was performed using Statistical Packages for Social Sciences (SPSS®; IBM®, Armonk, New York, United States) software. Baseline clinical characteristics were calculated using the Student's t test for continuous variables. The difference between the non-CKD, CKD Stage 1–4, and ESRD groups was analysed using Kruskal–Wallis test. Statistically significant trace element features were identified by evaluating element concentration and trends based ondiagnosis and severity of CKD. The intradialytic efficacy of the HD process was obtained by finding the difference between the pre- and post-HD blood concentration of participants with Stage 5 CKD undergoing chronic dialysis (CKD-5D):

$$\% \text{ Difference} = - \frac{\text{PreHDconc.} - \text{PostHDconc.}}{\text{PreHDconc.}} * 100$$

Spearman's correlation was used to evaluate correlations between trace element levels and age, serum creatinine, and eGFR. For the patients with Stage 5 CDK-HD, trace element correlations with length of HD sessions were also obtained. Partial correlations were adjusted for age and systolic BP to determine associations between trace elements, serum creatinine, and eGFR.

Using MetaboAnalyst 4.0, trace element data were log-transformed and auto-scaled by mean-centring and adding the standard deviation of each variable. Three algorithms, including support vector machines, partial least-squares discriminant analysis, and random forest, were used to generate models to identify the most significant trace element features. Multivariate logistic regression models were then constructed using the derived trace element features in models adjusted for age, sex, and hypertension. A p value of <0.05 was considered statistically significant.

RESULTS

Study Population

Study participants were predominantly of African descent (98%). The average age of the study participants was 51 years (range: 20–90). The average systolic BP of the study population was 146 mmHg (range: 96–235). The mean age, systolic BP, and blood glucose were highest among patients with Stage 5 CKD as compared to other study participants. In the study overall, there was an equal male–female distribution (50% each); however, there was a larger female representation within CKD Stages 1–4, while males accounted for twice the number of females in the CKD-5D group. Hypertension was the most common comorbidity for patients with CKD (87%), followed by diabetes (38%). Of the patients with CKD-5D, 85% attended bi-weekly dialysis sessions, 13% attended dialysis sessions three days per week, and 2% attended only one dialysis session per week.

Trace Element Analysis

Blood Sr levels progressively increased with declining kidney function (p<0.001). Table 1A shows other elements such as Cd (highest), Ba, and Si (lowest) in the patient group with CKD Stages 1–4 (p<0.001) as compared to the other groups; the table also shows Fe and Zn (highest), and Co (lowest) in the patient group without CKD as compared to the other groups (p<0.001). Linear progression models for geometric mean blood concentration for the first four stages of CKD produced a strong linear progression for Sr (r^2=0.96), and moderate/mild linearity for Si (r^2=0.65), Fe (r^2=0.63), Cd (r^2=0.63), Co (r^2=0.58), Ba (r^2=0.53), and Cr (r^2=0.51). However, most elements fit a polynomial trend better: Cu (r^2=31), As (r^2=0.16), Hg (r^2=0.15), Se (r^2=0.13), Zn (r^2=0.10), V (r^2=0.10), Pb (r^2=0.04), and Ni (r^2=0.00).

The following non-essential elements showed significant intradialytic changes: decreased As (46%; p<0.001) and increased Sr (56%; p<0.001). There was no significant difference in the mean essential trace element levels pre- and post-HD; however, Sr (r=0.362), Se (r=0.374), Pb (r=0.321), and Co (r=0.369) showed significant positive associations with length of HD in post-HD samples. Similarly, patients on thrice-weekly dialysis sessions were more likely to have increased Sr levels (r=0.273) compared to other patients on HD.

Table 1A: Trace element concentrations in whole blood for study participants.

Element	Group*	Geomean (µg/L)	SD (µg/L)	Median (µg/L)	Range (µg/L)		Group†
					Min	Max	
Sr	1	16.65	12.04	15.35	13.45	26.62	2>1‡
	2	38.03	18.26	40.04	17.24	82.83	3>1‡
	3	338.80	224.80	441.70	34.97	909.00	3>2§
Cd	1	0.46	0.85	0.44	0.05	3.54	2>1‡
	2	247.25	70.50	230.80	170.00	484.20	2>3‡
	3	1.13	1.31	1.31	0.06	6.83	3>1**
Ba	1	51.06	37.50	52.55	7.03	332.60	3>1**
	2	4.02	34.69	4.48	0.00	189.30	1>2‡
	3	72.63	77.10	81.00	9.20	161.40	3>2‡
Hg	1	1.35	1.52	1.18	0.37	9.85	3>1**
	2	0.43	0.39	0.46	0.02	1.71	1>2‡
	3	1.94	1.52	1.96	0.34	6.45	3>2‡
Pb	1	3.87	23.44	5.71	0.15	105.70	2>1**
	2	18.12	9.90	18.31	6.06	40.61	3>1‡
	3	21.97	23.44	29.52	0.01	19.51	3>2‡
As	1	1.01	1.20	1.12	0.10	4.30	2>1**
	2	4.78	4.68	4.41	1.12	22.36	3>1‡
	3	5.91	3.93	6.08	1.51	18.89	3>2‡
Ni	1	2.23	66.84	1.50	0.11	279.00	2>1**
	2	14.46	44.79	16.97	0.43	231.20	3>1‡
	3	12.15	29.59	11.10	3.06	149.90	2>3‡
Si	1	4,377.30	3,688.00	9,089.00	29.00	12148.00	3>1**
	2	1,059.00	715.70	982.40	152.00	3793.00	1>2‡
	3	8,124.40	2,760.00	7,917.00	4161.00	15218.00	3>2‡
Fe	1	414.58	82.28	428.60	221.10	592.80	2>3**
	2	394.81	70.13	408.90	200.20	511.70	1>3‡
	3	208.88	103.40	219.90	75.23	439.50	1>2‡
Zn	1	6.14	1.49	6.13	3.45	9.20	3>2**
	2	6.10	1.97	6.03	3.28	13.11	1>3‡
	3	4.12	1.76	4.12	1.93	8.65	1>2‡
Cu	1	1221.20	447.60	1,180.00	800.10	2,783.00	1>3**
	2	983.07	234.00	972.80	674.10	1,625.00	1>2**
	3	1,159.70	429.60	1,138.00	498.90	2,446.00	3>2**
Se	1	212.38	56.22	228.10	72.49	304.10	1>3**
	2	186.11	61.96	165.40	103.70	370.00	3>2§
	3	193.08	70.92	171.30	36.39	361.20	1>2**

Table 1A (Continued): Trace element concentrations in whole blood for study participants.

Element	Group*	Geomean (µg/L)	SD (µg/L)	Median (µg/L)	Range (µg/L)		Group†
					Min	Max	
Cr	1	21.46	18.54	44.38	0.65	56.97	3>1**
	2	12.02	30.62	12.23	1.02	153.50	1>2§
	3	23.49	37.03	35.31	3.04	146.70	3>2**
Co	1	0.67	1.11	0.52	0.05	5.69	2>1‡
	2	1.71	2.12	0.87	0.01	7.74	3>1§
	3	1.64	1.01	1.75	0.23	3.69	2>3**
V	1	4.00	3.67	7.28	0.04	13.59	3 > 1**
	2	2.46	11.36	2.60	0.31	58.41	3 > 2§
	3	6.36	3.27	7.76	1.40	13.59	1 > 2**

*Group 1: no CKD; Group 2: CKD Stage 1–4; Group 3: CKD Stage 5.

†Group comparison; group comparisons have an adjusted p value.

‡adjusted p value <0.001.

§adjusted p value <0.05.

**adjusted p value: no significance.

As: arsenic; Ba: barium; Cd: cadmium; CKD: chronic kidney disease; Co: cobalt; Cr: chromium; Cu: copper; Fe: iron; Hg: mercury; Ni: nickel; Pb: lead; Se: selenium; Si: silicon; Sr: strontium; V: vanadium; Zn: zinc.

Figure 1 shows the correlations between various trace elements and age. Three main correlation clusters were evident: firstly, V, Cr, Cu, Si, and Se, with Hg and Ba more distantly related; secondly, Pb, As, Ni, and Sr; and thirdly, Fe and Zn. Cd was an outlier. The first two clusters were more closely related than the third. Blood Sr was positively correlated with several non-essential elements including As (r=0.560; p<0.001) and Pb (r=0.550; p<0.001), but negatively correlated with essential elements such as Fe (r=-0.590; p<0.001) and Zn (r=-0.350; p<0.001). As a general finding, essential trace elements correlated positively with each other and negatively with non-essential elements. The exception to this trend was observed with Co, however, which correlated significantly with several non-essential elements including Pb, As, and Sr. The strongest correlations were observed between Fe and Zn (r=0.770; p<0.001), and Cd and Si (r=-0.720; p<0.001). The highest negative correlation was found between eGFR and Sr (r=-0.830; p<0.001). This significant correlation persisted after adjusting for age and systolic BP (r=-0.580; p<0.001). Non-essential metals such as Pb, Ni, As, and Hg all showed inverse association with eGFR, unlike Fe and Zn, which showed positive association. However, As (r=-0.403; p<0.001), Pb (r=-0.280; p<0.05), Fe (0.569; p<0.001), and Zn (0.301; p<0.05) remained significant after adjusting for age and systolic BP. Serum creatinine showed inverse relationships to Fe (r=-0.650; p<0.001) and Zn (r=-0.390; p<0.05), but a positive association with Sr (r=0.720; p<0.001) after adjusting for age and systolic BP.

All three algorithmic models ranked Sr in the top tier of the trace element profile. Further logistic regression analyses performed using partitioning of eGFR <60 mL/min/1.73 m^2 (Table 1B) and eGFR <45 mL/min/1.73 m^2 affirmed a significant association between CKD diagnosis and increased blood Sr levels. A receiver operator curve derived for Sr (Figure 2) showed the best cut-off for a CKD diagnosis at a Sr concentration of 22.90 µg/L (p<0.0001; standard error: 0.023).

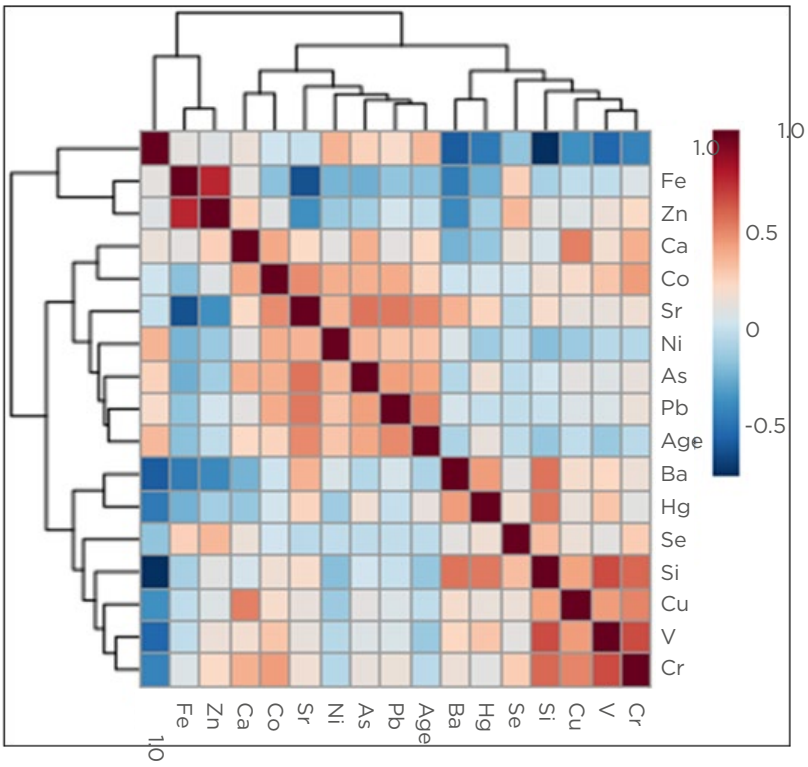

Figure 1: Heat map denoting correlations between age and trace elements.

As: arsenic; Ba: barium; Ca: calcium; Cd: cadmium; Co: cobalt; Cr: chromium; Cu: copper; Fe: iron; Hg: mercury; Ni: nickel; Pb: lead; Se: selenium; Si: silicon; Sr: strontium; V: vanadium; Zn: zinc.

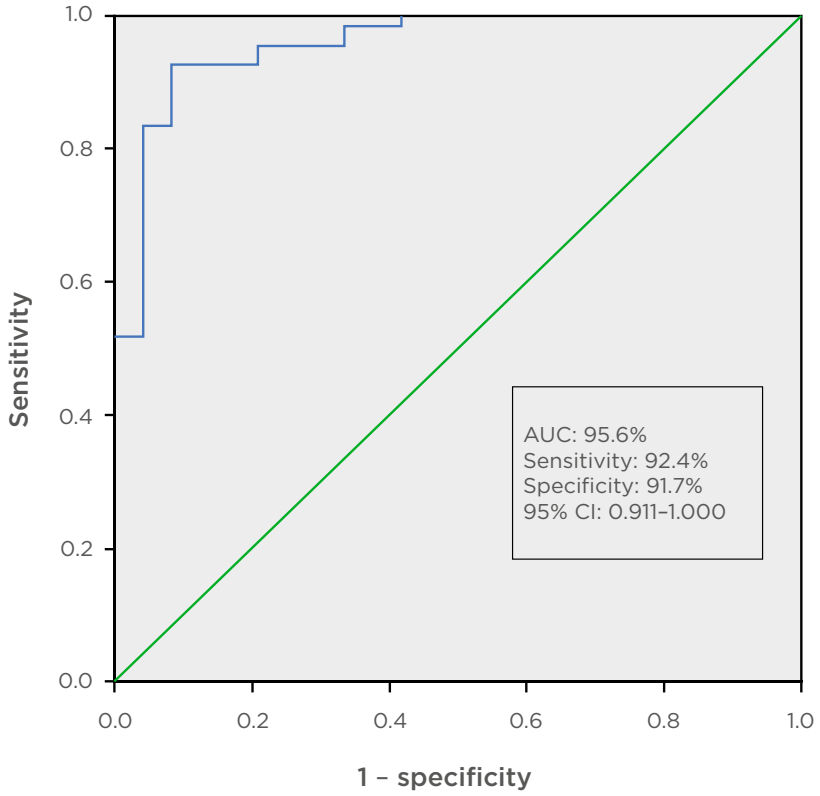

Figure 2: Receiver operator curve for strontium as a potential marker for chronic kidney disease.

AUC: area under the curve; CI: confidence interval.

Table 1B: Significant features of trace elements and odds ratio with chronic kidney disease.

Variables	Odds ratio (95% CI)	Significance	Model parameters
Univariate model			
Blood Pb	2.838 (0.644–12.505)	0.168	N/A
Blood Cd	3.437 (0.770–15.341)	0.106	
Blood Sr	14.618 (2.840–75.237)	0.001	
Blood As	3.100 (0.762–12.617)	0.114	
Blood Fe	0.836 (0.149–4.691)	0.838	
Blood Zn	0.181 (0.032–1.035)	0.055	
Multivariate model 1			
Blood Sr	24.229 (5.810–101.040)	<0.001	Model fitting: significant Goodness of fit†: no Significant predictors (LR): Sr, Cd Predictive accuracy: 79.8%
Blood Cd	3.621 (1.006–13.034)	0.049	
Blood Pb	2.221 (0.664–7.421)	0.195	
Multivariate model 2			
Blood As	4.756 (1.397–16.191)	0.013	Model fitting: significant Goodness of fit†: yes Significant predictors (LR): As, Sr Predictive accuracy: 82.0%
Blood Sr	14.871 (4.008–55.176)	<0.001	
Blood Pb	1.962 (0.564–6.823)	0.289	
Multivariate model 3			
Blood Sr	11.672 (2.749–49.551)	0.001	Model fitting: significant Goodness of fit†: no Significant predictors (LR): As, Age, Sr Predictive accuracy: 92.0%
Age	15.992 (3.713–68.886)	<0.001	
Blood As	5.969 (1.441–24.721)	0.014	
Multivariate model 4			
Blood Sr	9.895 (1.939–50.485)	0.006	Model fitting: significant Goodness of fit†: mixed Significant predictors (LR): As, Sr Predictive accuracy: 90.9%
Blood As	6.294 (1.078–36.753)	0.041	

*Compares the full model containing all the predictors against a null model.

†Contains deviance and Pearson chi square tests. A mixed result indicates features do not agree on whether the data fits the model well.

Median cut-off levels for each variable: Pb (17.57 µg/L); Cd (1.94 µg/L); Sr (40.63 µg/L); As (4.08 µg/L); Fe (362.9 µg/L); Zn (5.94 µg/L). Multivariate models follow top-ranking features derived in previous analysis. Multivariate model 4: adjusted for age, gender, and systolic blood pressure.

As: arsenic; Cd: cadmium; CI: confidence interval; Fe: iron; LR: likelihood ratio; N/A: not applicable; Pb: lead; Sr: strontium; Zn: zinc.

DISCUSSION

This study found that blood Sr levels increased significantly with a corresponding decline in kidney function. Blood Sr levels rose in patients with CKD-5D even after HD, suggesting a veritably higher exposure risk as compared to subjects without CKD. The strong linear progression with increasing severity of kidney disease and associations with HD treatments strongly suggest that the cumulative trend is associated with increased retention of Sr because of interventional treatment peculiar to patients with ESRD. A similar finding by Schrooten et al.[22] reported significantly high Sr levels in a study involving 34 dialysis centres and mainly attributed uptake to be from dialysate fluid or from administration of vitamin D supplements and phosphate binders. If so, patients on HD would be more vulnerable to Sr exposure due to increased renal retention and chronic intake of dietary supplements and medications that contain Sr. In healthy individuals, Sr is preferentially excreted over calcium (Ca) despite being absorbed at lower levels by comparison; however, in CKD, as renal excretion of Sr declines, excretion rates become comparable to that of Ca and competes with Ca for bone absorption.[23-25] Under the deficient conditions of Ca, vitamin D, and/or phosphorus and reduced serum protein, Sr absorption increases and can precipitate strontium rickets.[26,27] As a strong precedent has been set for its involvement in osteoporosis and fracture risk assessment, the association between Sr and mineral bone disease is an equally relevant cause for further research. What is evidently a direct relationship between Sr and kidney disease is extremely promising as a potential marker.

Pb and Cd also compete with Ca for the binding sites on transport proteins; however, they do not have the equivalent ionic mimicry that Sr has with Ca.[28] A series of studies performed by the National Health and Nutrition Examination Survey (NHANES), Centers for Disease Control and Prevention (CDC), showed positive associations between nephrotoxins Cd and Pb and CKD, including Navas-Acien et al.[29] and Ferraro et al.[30] who demonstrated an inverse relationship between Cd and Pb and CKD, and direct associations of Cd with albuminuria and eGFR. Buser et al.[12] confirmed these findings, relating inverse relationships of Pb and Cd to eGFR.[12] However, Kim et al.[31] found that only exposure of Cd was associated with CKD risk in patients from Korea with diabetes or hypertension, despite registering higher mean blood levels of Cd and Pb as compared to their counterparts from the USA. Differences in sources of exposure and genetic make-up, among other factors, may explain these discrepancies. In some models, eGFR was also inversely related to blood As. When investigating As, the Strong Heart Study[29] revealed significantly lower urinary excretion rates of As in patients with CKD, suggesting retention of the trace element was a factor in As. Palaneeswari et al.[32] suggest that their results showing elevated As in 50 patients with ESRD may be the cumulative effect of decreased renal excretion, among other reasons.

These trace elements have known nephrotoxic potential and a strong affinity for renal tissue, employing different mechanisms by which they interact and interfere with resident signalling molecules, transport proteins, and organelle function to cause kidney injury.[33,34] Like Buser et al.,[12] the present study concludes that reverse causality is primarily responsible for the overall increase of non-essential element levels observed in patients with CKD. Simply put: reduced excretion results in increased retention. Other mechanisms may be at play, selectively increasing Sr blood levels in comparison to that of other non-essential elements; however, the inverse relationship with eGFR can be utilised to monitor kidney function.

The reports on comparative trends of essential elements were generally more diverse. In this study, only Fe and Zn showed initial significant associations with CKD. However, after adjustments for age, sex, and BP, these associations were not statistically significant. Consequently, the purported accumulation of Cr and V reported in other studies was not observed in this study. Tonelli et al.[16] in a meta-analysis of 128 studies (patients per study ranged from 6 to 456 patients; median: 24) determined that Cu, Cr, and V blood levels were increased in patients on HD, while decreased Se and Zn trends were common. Another review by Jankowska et al.[35] contended that decreased Zn and Se and elevated Cu levels are associated with CKD. However, previous studies by Prodanchuk et al.,[36] which did not include Fe levels, reported

an increase in Cu (p=0.114), Cr (p<0.001), Zn (p<0.001), and V (p<0.001) and a decrease in Se (p<0.05) in 41 patients with ESRD. Dlugaszek et al.[37] countered with an investigation of Fe, Zn, Cu, and Cr in serum, erythrocytes, and hair from 31 patients. While elevated levels of Cr (p<0.001) and Fe (p>0.05) were displayed in each measurement, the inverse trend (p>0.05) was apparent in hair (decreased Zn and increased Cu) when compared to serum and erythrocytes. Lokesh et al.,[38] conversely, reported decreases in Se (p=0.217) and increases in Cr (p<0.001) in 40 patients with ESRD; Fe, Zn, V, and Cu were not included in this analysis. Raoofi et al.[39] claimed significant decreases in both serum Cu and Zn in patients with ESRD, while Balla and Ismail[40] concluded HD increased serum Zn and decreased serum Cu, though Zn levels remained deficient in ESRD as compared to controls.[39,40]

The phenomenon of interrelationships between trace elements was observed in this study. Generally, the authors postulated that antagonistic relationships between and among trace elements were partly responsible for their observations apart from the eGFR. Few studies have evaluated the significant clinical outcomes associated with those trace element findings; however, Tonelli et al.,[17] in a prospective longitudinal study, evaluated several clinical outcomes and reported significant associations between risk of mortality and increased hospitalisations with lower concentrations of Se.[17]

Generally, lower levels of trace elements with protective biological properties such as Fe, Zn, and Se are observed in patients with chronic diseases, a consequence of increased mobilisation to counter oxidising events precipitated by or causing chronic disease.[41] As a consequence, diminished levels of essential elements increase the susceptibility for infection, oxidative stress, and proinflammatory processes.[35,42,43] The non-linear trends observed indicate a more complex interplay in the pathophysiology of CKD and inadequate recovery mechanisms in more severe disease, as well as antagonistic relationships with non-essential elements.

This study's findings provide a compelling case to pursue validation and/or classification studies for the association of Sr as a biomarker of CKD.As this was the first trace element profiling study carried out among patients with CKD in Jamaica (and the wider Caribbean region), this study provided unique insight to previously unknown associations, and the collaborative framework established during this study provides an optimistic outlook for follow-up studies. However, the lack of funding presented the greatest challenge and limited the sample size of the study population. This prohibited the involvement of participants from rural parishes bordering the island, particularly to the west. As a result, study findings cannot be applied to the entire CKD population in Jamaica. Furthermore, the cross-sectional design of the study does not allow the case for causation to be made. It also does not adequately explore the potential risk for progression of CKD. While it can provide a baseline for further work, a longitudinal approach to investigate trace element levels in relation to the decline of kidney function would better capture this relationship. In so doing, related adverse health outcomes can be assessed as secondary endpoints. Additionally, parameters that may contribute to the trace element constitution of subjects should be accounted for in future studies. These include lifestyle habits, occupational exposure, and drug exposure, amalgam or prosthetic use.

Data related to recreational/prescription drug and oral supplement intake and other therapeutic options used by patients with CKD should also be accounted for, particularly those highlighted in studies as potential sources of exposure. Exposure assessment should include phosphate binders, vitamin D, and other commonly consumed dietary supplements and a comprehensive trace element profile of dialysate fluid used during HD therapy. The prevalence of CKD and seasonal and dietary factors should also be evaluated for their potential role in observed trace element trends in the general population. It may be that trace element profiles for CKD vary based on geographical locations. As such, national biomonitoring surveys should be performed to establish reference intervals to permit the identification of abnormal trace element findings and subsequent classification as excess or deficient levels accordingly.

CONCLUSION

The association between blood Sr and CKD has not been a finding widely discussed in published

work. Certainly, in the Caribbean it is a novel concept that could expand the use of the trace element profiles in the biomarker analysis of CKD, particularly if these associations are independent of external factors unrelated to the disease pathophysiology. Researchers in the region should be encouraged to explore further trace element relationships, and perform risk analysis of high-risk groups for chronic disease and potential sources of exposure to non-essential and nephrotoxic trace elements.

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The Non-coding MicroRNA-223 is a Promising Biomarker of Chronic Kidney Disease

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Abstract

Renal diseases are consecutive to a deregulation of gene expression regulated by non-coding RNAs. These non-coding RNAs were discovered at the turn of the 21st century when it was established that post-transcriptional regulation was performed through small non-coding RNAs, known as microRNAs (miRNAs). Up to 3,000 miRNAs are expressed by human cells. They are small, single-stranded nucleic acids, which trigger translational repression of mRNA by base-pairing with the 3′ untranslated region of their mRNA targets. In addition to miRNA regulation, it was also demonstrated that 60,000 long non-coding RNAs are expressed in the human cell and that they are able to regulate gene expression at all levels. The roles of these various RNA families are just beginning to be understood in the field of nephrology. In the past decade, the authors and various others have published that several miRNAs are deregulated during the onset of chronic kidney disease (CKD) and are associated with cardiovascular damage. This review focuses on miRNA-223 (miR-223) as its expression is increased *in vivo* in the large vessels of a mouse model of CKD, whereas it is diminished in the serum of both mice and human patients with CKD. In patients, miR-223 expression was correlated with all-cause mortality, as well as cardiovascular and renal events. Molecular clues were given by a multi-omics approach, indicating that miR-223 modulates gene regulation at all levels including mRNA expression, protein amounts, and metabolic molecule accumulation. miR-223 is thus a potential target to prevent or treat complications of CKD pathogenesis.

INTRODUCTION

RNAs are currently a much-discussed molecular species. They can be used as vaccines, as extensively shown during the COVID-19 crisis,[1] but could also be at the very origin of life on our planet. Indeed, Walter Gilbert coined the term 'RNA world' in 1986 to suggest that self-replicating RNA molecules were at the very origin of life during evolution, before the appearance of DNA and proteins.[2,3] These RNAs, several billions of years later, would be at the origin of the increasing number of RNA species that are instrumental in gene regulation.[4] Short non-coding RNA species such as microRNAs (miRNAs) were discovered at the onset of the 21st century.[5,6] The recent progress in deep sequencing has now shown that, contrary to what most molecular biology books describe, a vast majority of the eukaryotic genome is

transcribed, and that a complex network of long and short transcripts, including tens of thousands of non-coding RNAs, is central to our metabolism. These findings extend far beyond the DNA–RNA–protein central dogma published by Francis Crick in 1957.[7] All these non-coding RNAs are increasingly studied by the authors and numerous others as innovative biomarkers but also as innovative therapeutic targets.

THE ROLES OF NON-CODING RNA IN THE FIELD OF NEPHROLOGY

Patients with later-stage chronic kidney disease (CKD) exhibit a high cardiovascular morbimortality associated with cardiovascular disease (CVD).[8] CVDs account for 30% of all global deaths and are particularly devastating in the course of CKD.[9] A majority of fatalities are caused by atherosclerosis, a pathological process that will impact any artery. Due to the intricacy of the pathophysiological process, it is thought that non-traditional predictive factors for CVD complications would be useful for prognosis and diagnosis.

miRNAs represent a new class of biomolecules, endogenous interfering RNAs, which are now considered promising biomarkers for numerous pathologies.[5] They are non-coding RNAs that contain approximately 20–25 nucleotides and precisely regulate gene expression, thereby affecting the stability and translation of mRNAs in a post-transcriptional manner.[5] Their number is now estimated to be approximately 2,000–3,000 and the reciprocal genes represent approximately 3% of the genome.[5,10] miRNA precursors are derived from longer primary transcripts termed pri-miRNAs. These are cut in the nucleus by the Class 2 ribonuclease (RNase) III enzyme Drosha into a precursor miRNA hairpin (60–70 nucleotides). The hairpin then migrates into the cytoplasm by way of exportin 5. Dicer RNase III subsequently cuts the hairpin it into a double-stranded RNA, comprising the 5' and 3' strands, and will in turn bind the RNA-induced silencing complex. This multi-molecular complex unwinds the RNA into single-stranded RNA, known as the mature miRNA, and directs it to the target mRNAs, which triggers gene silencing.[5] Human miRNAs mostly act by destabilising their target mRNAs to diminish translation levels.[6] It is now documented that the 2,000–3,000 miRNAs alter the expression of approximately one-third to two-thirds of the human genome.[6] This is explained by the fact that mismatches are present in the binding sites between miRNA and mRNA targets and, therefore, a miRNA can bind dozens of different messenger RNAs and attenuate the expression of as many genes.

Since their discovery, it has been understood that miRNAs could be useful tissular biomarkers, however, their use was precluded for most diseases because biopsies were not accessible to biologists. Fortunately, since 2008 we have known that miRNAs also circulate and are stable in human blood.[11,12] This makes them useful as non-invasive biomarkers as a simple blood sample is enough to assess their expression,[10] and several studies in the field of oncology have shown a link between miRNA seric levels and tissue amount.[11] miRNAs are present in microvesicles or complexed with chaperone proteins that protect them from RNase activity,[13] emphasising their roles as potential non-invasive biomarkers. A pioneering study from De Rosa et al.[14] showed that miRNA levels are different in the serum of patients with coronary artery diseases compared to patients who are healthy. An accurate amount of a spike-in exogenous, synthetic *Caenorhabditis elegans* miRNA-39 miRNA is mostly used as reference in order to avoid further experimental bias.[12]

THE IMPORTANCE OF MICRORNA-223 IN CHRONIC KIDNEY DISEASE

CKD is characterised by a slow and progressive loss of kidney function, leading to vessel and bone damage. It has been shown that miRNAs are involved in the pathophysiology of CKD;[10,15,16] for example, they play an important role in controlling vascular smooth muscle cell trans-differentiation during vascular calcification, which is a complication of CKD.[16,17] This would imply that miRNAs are critical players in the differentiation of vascular cells in CKD-related CVD.

The authors were the first group to show that miR-223 expression levels were modulated in pathological vessels and blood of a CKD mouse model.[17,18] In the aorta, miR-223 levels were doubled in the mice with CKD, whereas they almost tripled in *ApoE*-knockout rodents that suffered from CKD, displaying vascular

calcification.[17] Conversely, the authors showed that miR-223 seric levels diminished during CKD in all pathological mice;[17] this finding was confirmed in a large CKD patient cohort, which will later be discussed.[19] Additionally, in the murine study, the authors published that the calcium-free phosphate binder sevelamer carbonate alleviated the miRNA deregulations in aortas, suggesting a possible direct link between the observed miRNA alterations and vascular calcification formation.[8] This is interesting in light of miR-223's role in osteoclast differentiation, suggesting that this RNA has an effect on the vascular calcification and osteoporosis process.[20]

In view of miR-223 expression in the media of the aorta, the authors also observed the expression in the intima (Figure 1). In the intima, miR-223 is strongly expressed in freshly isolated endothelial cells but its levels decrease very quickly during cell subculture.[21] This suggests that miR-223 is not produced in endothelial cells but is imported from other cell types, such as monocytes and macrophages. Tabet et al.[22] also showed that high-density lipoproteins can deliver miR-223 to endothelial cells. Additionally, the authors published that miR-223 is expressed in freshly isolated endothelial cells from the brain microvasculature.[18] The important increase of the inflammatory miR-223 expression during the course of CKD in both the intima and media could thus induce chronic low-grade inflammation and atherosclerosis. Recent results from the authors in a rat model of restenosis suggest that an increase in miR-223 is detrimental and that an anti-miR antisense strategy against miR-223 decreases restenosis (Figure 2).[23]

MICRORNA-223 AFFECTS SEVERAL LEVELS OF GENE REGULATION

A multi-omics study enabled the authors to estimate the influence of over-expression and inhibition of miR-223, a pleiotropic regulator of metabolic-related disease, in a monocyte-macrophage cell line.[24] Using a combination of microarray transcriptomics, SELDI-TOF and MALDI-TOF proteomics, and nuclear magnetic resonance-based metabolomics, the authors estimated the levels of proteins, mRNAs, and metabolites to identify genes involved in miR-223 regulation, hypothesising that the deregulated molecules would be candidate disease biomarkers and potential therapeutic targets.

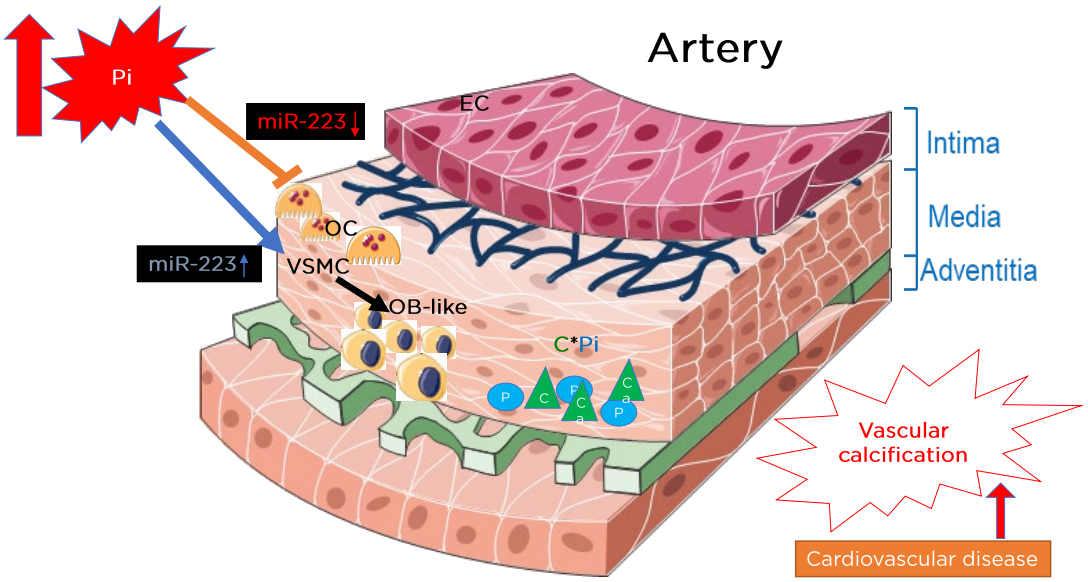

Figure 1: The instrumental role that miR-223 plays on the effects of inorganic phosphate on both VSMC trans-differentiation and vessel osteoclastogenesis, inducing vascular calcification.

C: calcium; EC: endothelial cells; miR-223: microRNA-223; OB: osteoblasts; OC: osteoclasts; P: phosphate; Pi: inorganic phosphate; VSMC: vascular smooth muscle cells.

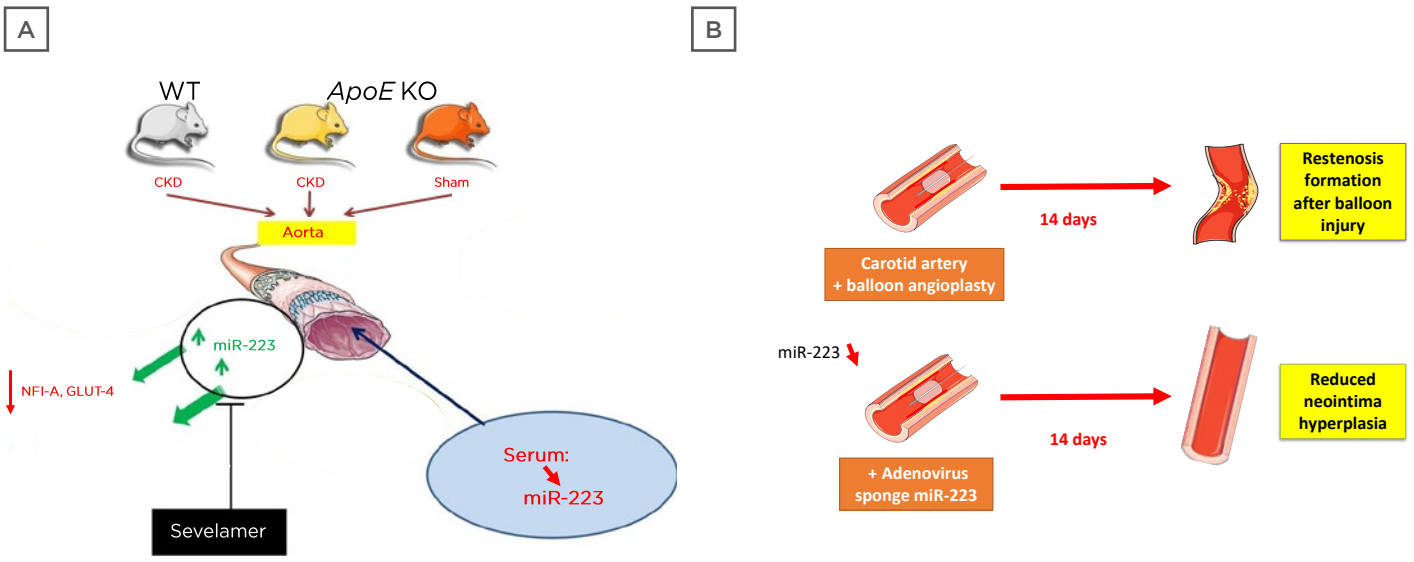

Figure 2: Pre-clinical models explaining the effects of microRNA-223 *in vivo* on cardiovascular events linked to vascular calcification.

A) Murine model of CKD and atherosclerosis (*ApoE* knockout). Mice with both CKD and *ApoE* knockout display vascular calcifications. **B)** Rat restenosis model. Sponge treatment decreases miRNA-223 levels and diminishes restenosis in the carotid.

CKD: chronic kidney disease; GLUT-4: glucose transporter Type 4; KO: knockout; miR-223: microRNA-223; NFI-A: nuclear factor I A-type; WT: wild type.

They found that 52 proteins were significantly altered when comparing scramble and pre- and anti-miR223 treatment. Among these, the transcription factors CARM1, UBE2G2, Cactin, and NDUFAF4 were involved in the stability of mRNAs, bone remodelling, and immune response. Transcriptomics showed changes in the expression of 120 genes, among which 30 genes encoded for long non-coding RNAs. Representative genes were again implicated in bone remodelling and RNA regulation. The most deregulated metabolites were linked to metabolism and pyrimidine nucleotides.

MICRORNA-223 CAN BE A PREDICTOR OF CHRONIC KIDNEY DISEASE PROGRESSION

Levels of several miRNAs could be associated with CKD progression;[10] however, their association with clinical outcomes remained only partly understood. To gain further insight, the authors recently measured serum levels of miR-223 and miR-126 in a cohort of 628 patients (patients with CKD Stage 1–5 or patients on renal replacement therapy [CKD 5D], and healthy controls) in collaboration with the Ghent University Hospital, Belgium. In this large cohort, patients with CKD were followed over 6 years, tracking all-cause mortality and cardiovascular and renal events.[19] The serum levels of miR-223 were significantly lower in the CKD Stage 3B–CKD 5D groups than in the control group. Seric levels of miR-126 were significantly lower in the CKD Stage 2–CKD 5D groups than in the controls. Concerning events were that patients with below-median levels of miR-223 and miR-126 had the lowest survival rate. CKD is thus associated with a decrease in circulating miR-223 and miR-126 levels in humans with impaired kidney function. Neither miR-223 nor miR-126 was a prognostic marker of all-cause mortality, cardiovascular events, or renal events, as associations between miRNA levels and overall mortality were not significant when results were adjusted for baseline estimated glomerular filtration rate. The mechanism that underlies the low expression of circulating miRNAs in CKD has yet to be identified.

There are thus several limitations to the use of miRNAs as biomarkers in the area of CKD. Currently, they are no better than the estimated glomerular filtration rate gold standard and,

therefore, other candidates will have to be identified. They are also not tissue-specific as miR-223 is expressed in skeletal muscle[25] as well as the kidney.

CONCLUSION

miRNA regulation during the course of CKD is a complex process as these small non-coding RNAs are expressed in a cell- and tissue-specific manner. Additionally, the existence of long non-coding RNAs has reshaped our view on gene regulation, increasing its complexity even further. We are now at a stage where non-coding RNA expression can be studied in human CKD populations, before and after the appearance of vascular disease, in order to develop them as new biomarkers, useful for diagnosis and treatment evaluation, but also to detect innovative targets for future therapeutic strategies.

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The Role of Dexmedetomidine for the Prevention of Acute Kidney Injury in Critical Care

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Abstract

Acute kidney injury (AKI) occurs in up to 50% of patients admitted to the intensive care unit and is associated with increased mortality. Currently, there is no effective pharmacotherapy for prevention or treatment of AKI. In animal models of sepsis and ischaemia-reperfusion, α2-agonists like dexmedetomidine (DEX) exhibit anti-inflammatory properties and experimental data indicate a potential protective effect of DEX on renal function. However, clinical trials have yielded inconsistent results in critically ill patients. This review discusses the pathophysiological mechanisms involved in AKI, the renal effects of DEX in various intensive care unit-related conditions, and summarises the available literature addressing the use of DEX for the prevention of AKI.

INTRODUCTION

Acute kidney injury (AKI) is defined by a rapid rise in serum creatinine, a drop in urine output, or both, and occurs in up to 15% of patients who are hospitalised and up to 50% of patients admitted to the intensive care unit (ICU).[1] Major surgery, cardiac surgery, sepsis, cardiorenal, and hepatorenal syndrome are among the most frequent risk factors in critically ill patients. AKI is often part of a syndrome rather than a single pathophysiological entity, and the pathophysiology varies according to the underlying causes and pre-existing conditions. Renal hypoperfusion can occur due to hypovolaemia, systemic vasodilatation, increased vascular resistance, cardiac dysfunction, or increased intra-abdominal pressure leading to venous congestion. Renal hypoperfusion activates adaptive mechanisms such as vascular autoregulation and stimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone system to maintain glomerular filtration rate (GFR). With prolonged hypoperfusion or inadequate adaptive mechanisms, GFR initially drops without structural damage to the renal parenchyma. However, ischaemic acute tubular necrosis occurs if renal perfusion remains compromised. Likewise, nephrotoxic drugs and endogenous

toxins like myoglobin and uric acid can have a direct cytotoxic effect, compromise intrarenal haemodynamics, and cause precipitation of crystals or metabolites.[2] Nearly two-thirds of AKI cases resolve within a week and in such patients, 12-month survival is over 90%. However, if AKI does not resolve, hospital mortality is significantly increased (47%) and 12-month survival is only 77%.[3] Currently, there is no effective pharmacotherapy for prevention or treatment of AKI. Prevention bundles emphasise risk stratification and avoidance of hypotension, hypoperfusion, and refrainment from nephrotoxic substances.[4]

Dexmedetomidine (DEX) is a centrally acting, highly-selective α2-adrenergic agonist and has become an increasingly popular sedative agent in critical care due to its sedative, anxiolytic, sympatholytic, and analgesic-sparing effects, with minimal depression of the respiratory drive.[5] Side effects comprise hypertension, hypotension, bradycardia resulting from vasoconstriction, sympatholytic effects, and baroreflex-induced parasympathetic activation.[6,7]

DEX is rapidly distributed and is mainly hepatically metabolised into inactive metabolites by glucuronidation and hydroxylation. Compared with classic sedatives like propofol and benzodiazepines, DEX provides lighter levels of sedation and supplemental analgesic effects.[8] Patients remain easily rousable with minimal influence on respiratory drive. Moreover, DEX attenuates stress responses, creating a more stable haemodynamic profile during stressful events such as surgery or anaesthetic induction.[9-12] Finally, DEX improves sleep efficiency and quality.[13-14]

The main advantage of DEX in patients in the ICU is reduction in the incidence of delirium[15] and duration of mechanical ventilation.[16] The use of DEX has been recommended over benzodiazepines in patients who are mechanically ventilated as it may be associated with improved outcomes.[8,17-19] Clinical trials have also demonstrated that DEX-based sedation provides some advantages over usual care, typically with propofol, lorazepam, or midazolam. These advantages include a reduction in the duration of sedation and ICU stay and a possible effect on reducing the duration of delirium.[8,20-22] The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial compared DEX with lorazepam.[21] Sedation with DEX resulted in more time at the targeted level of sedation and more days alive without delirium or coma (median days: 7.0 versus 3.0; p=0.01) and a lower prevalence of coma (63% versus 92%; p<0.001). The Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) trial compared DEX to midazolam.[22] The prevalence of delirium was 54% in the DEX group versus 76.6% in patients treated with midazolam, for a difference of 22.6% (95% confidence interval: 14–33%; p<0.001). Median time to extubation was 1.9 days shorter in the DEX group (3.7 days versus 5.6 days; p=0.01). The multicentre, double-blind, placebo-controlled Dexmedetomidine versus Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation (MIDEX and PRODEX trials),[8] compared DEX with midazolam and propofol and demonstrated the safety and non-inferiority of DEX as a first-line sedative in patients who were critically ill and on ventilation. Median duration of ventilation was shorter with DEX (123 hours; interquartile range [IQR]: 67–337]) versus midazolam (164 hours; IQR: 92–380; p=0.03) but not with DEX (97 hours; IQR: 45–257) versus propofol (118 hours; IQR: 48–327; p=0.24).[8] Finally, the pivotal Sedation Practice in Intensive Care Evaluation (SPICE III) trial[23] randomised 4,000 patients to receive either DEX as the sole or primary sedative or to receive usual care (propofol, midazolam, or other sedatives). Sedation with DEX did not affect overall mortality or mortality in key clinical predefined subgroups. However, it showed statistically significant heterogeneity of treatment effect according to age: DEX-based sedation appeared to increase 90-day mortality in patients below the median age of 63.7 years (relative risk increase of 23.7%) and to decrease mortality in patients older than the median trial age (relative risk reduction of 11%).[24]

α2-agonists like DEX exhibit anti-inflammatory properties and have been ascribed respiratory, cardiac, neurologic, and renal protective effects.[25] Moreover, DEX inhibits the antidiuretic action of vasopressin,[26] enhances osmolal clearance, and preserves cortical blood flow by decreasing renal cortical release of noradrenaline (Figure 1).[27] However, the relevance and

effect of these effects on clinical outcomes remains uncertain. In this narrative review the authors address the putative reno-protective effects of DEX and summarise the results from clinical and animal studies addressing the use of DEX for the prevention of AKI.

THE ANTI-INFLAMMATORY EFFECTS OF DEXMEDETOMIDINE

DEX inhibits toll-like receptor-4/NFκB pathway activation and therefore decreases the production of proinflammatory cytokines such as TNF-α and IL-6.[28-30] These actions are mainly mediated by α2-adrenergic receptor subtypes[29,31] although other adrenergic-receptor-independent mechanisms,[28] vagomimetic, and humoral pathways contribute to the anti-inflammatory effect.[32-34] DEX also reduces oxidative stress by attenuating the formation of reactive oxygen species, increasing glutathione levels, inhibiting oxygen consumption, and improving mitochondrial dysfunction.[35,36] Finally, DEX has been reported to promote resolution of inflammation through activation of so-called specialised pro-resolving lipid mediators.[37] Among these, lipoxin A4 is one of the most important, and its biosynthesis depends on 5-lipoxygenase and adrenergic receptor activity. Lipoxygenase-5 and lipoxin A4 expression are increased in DEX-treated animals with sepsis, providing evidence that DEX not only inhibits the generation of excessive inflammation but also enhances its resolution.[38]

DEXMEDETOMIDINE FOR THE PREVENTION OF ACUTE KIDNEY INJURY IN CARDIAC SURGERY

AKI affects up to 30% of patients undergoing cardiopulmonary bypass (CPB) surgery and is the second most common cause of AKI in the ICU.[39] Patients undergoing cardiac surgery are particularly at risk, as factors like non-pulsatile perfusion during CPB, hypothermia, coagulopathy, haemolysis, activation of cytokines, complement pathways and the renin-angiotensin-aldosterone system, and pituitary secretion of arginine-vasopressin in response to low-flow states result in microcirculatory and renal vasoconstriction.

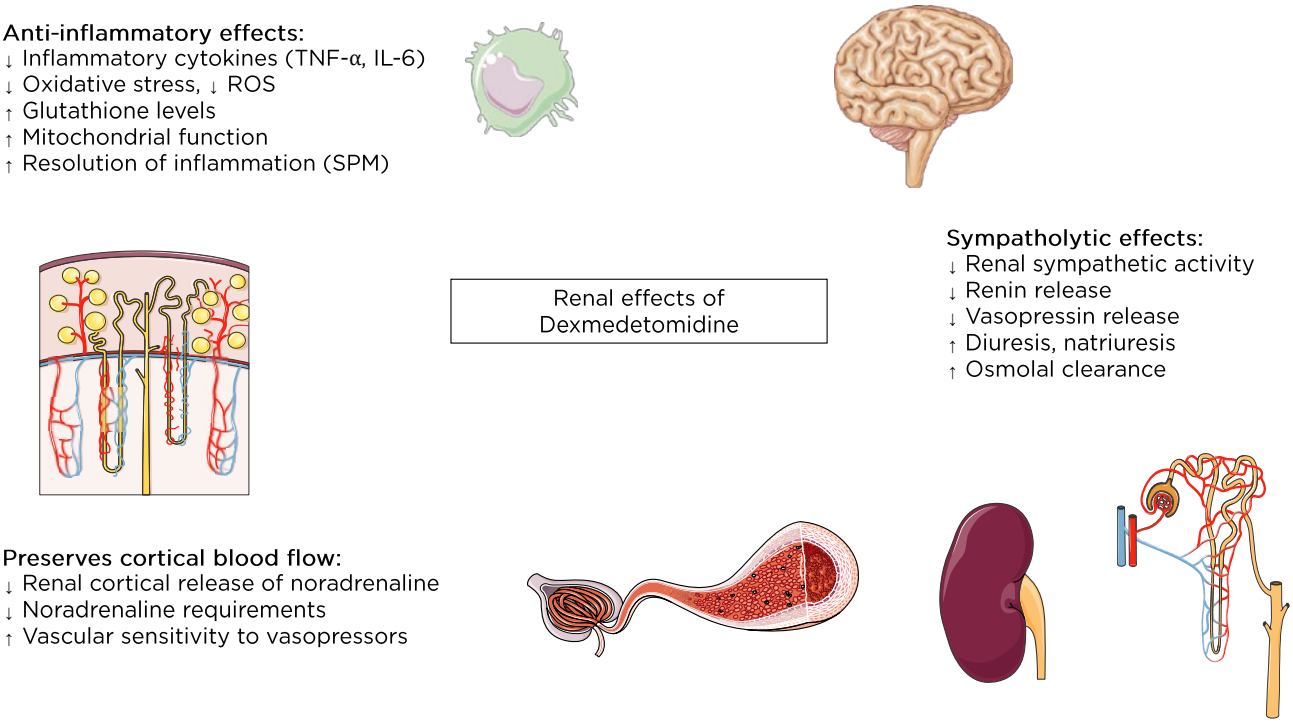

Figure 1: Overview of the renal effects of dexmedetomidine.

ROS: reactive oxygen species; SPM: specialised pro-resolving mediators.

Moreover, release of aortic cross-clamping leads to reperfusion injury and further cellular damage.[1]

Clinical and animal studies point towards a protective effect of DEX against AKI in this setting. In rodent models of ischaemia-reperfusion (I-R), intraperitoneal administration of DEX at doses between 10 and 100 µg/kg reduced inflammation and histomorphological signs of renal injury.[31,34,40-45] However, these protective effects could not be replicated in studies where DEX was given intravenously (dose range: 1–3 µg/kg/hour).[46,47] Nevertheless, in patients undergoing cardiac surgery, DEX appears to decrease the incidence of postoperative AKI. Several clinical trials have assessed the effect of DEX in this patient population, and DEX improves traditional[48] and modern renal biomarkers[49,50] and renal function in most studies.[51,52] A meta-analysis and trial sequential analysis of nine randomised controlled trials (RCTs) with a total of 1,308 patients found robust evidence that DEX significantly reduced the incidence of AKI after cardiac surgery (risk ratio: 0.60; 95% confidence interval: 0.41–0.87; p=0.008).[53] The protective effect on AKI was most evident when DEX was administered pre- or intraoperatively and in patients aged over 60 years. DEX also reduced time to extubation and incidence of delirium. There were no significant differences in other postoperative complications, urine output, length of ICU stay, and mortality. Compared to the earlier meta-analyses,[54,55] summarised in Table 1,[53-56] the study by Peng et al.[53] used a more robust and transparent methodology. However, as the studies included in this systematic review covered nearly a decade, different definitions of AKI were used. Therefore, the effect of DEX on incidence of AKI after cardiac surgery under a common definition remains unclear.

Several factors need to be considered when interpreting the results of trials and meta-analyses addressing the role of DEX for prevention of AKI. Many patients undergoing cardiac surgery have pre-existent renal dysfunction or comorbidities that make the kidneys more vulnerable to injury. As outlined above, the CPB procedure itself, aortic cross-clamping time, transfusion of blood products, high doses of vasopressors, and inotropes all contribute to the development of postoperative AKI. Therefore, any baseline variability regarding these factors between trial participants may significantly undermine the value of a meta-analysis. The potential protective role of DEX in AKI can only be appreciated when timing and dose of the intervention, type and duration of surgery, patient characteristics, and perioperative therapeutic strategies are considered.

DEXMEDETOMIDINE FOR THE PREVENTION OF ACUTE KIDNEY INJURY IN NON-CARDIAC SURGERY

Postoperative AKI affects approximately one-fifth of patients after major surgery.[57] Major surgery is among the most common risk factors for AKI, as it frequently implicates significant shifts in intravascular volume, transient hypotension, and the exposure to nephrotoxic substances including contrast media, antibiotics, and non-steroidal anti-inflammatory drugs. Increased levels of circulating cytokines and reactive oxygen species due to endotoxins from compromised visceral perfusion and I-R injury contribute to renal injury.[58] Furthermore, advanced age and pre-existing comorbidities including diabetes, chronic renal failure, and heart failure increase the risk for developing AKI,[1] and complex surgical interventions are performed in older and sicker individuals, thus increasing numbers of patients at risk.[59]

Experimental and clinical data on the effect of DEX on postoperative AKI in non-cardiac surgery are rare (an overview of relevant studies in humans is given in Table 2).[20,60-63] In a rat model of orthotopic liver transplantation, intraperitoneal DEX (10 µg/kg) decreased blood urea nitrogen (BUN) and serum creatinine levels and reduced histopathological kidney injury.[29] However, in a single-centre retrospective cohort study of 1,207 patients, the use of intraoperative DEX was not associated with a decline in AKI after lung cancer surgery. A pilot RCT of 89 patients undergoing laparoscopic radical prostatectomy found that, compared to normal saline, an intravenous bolus of 1 µg/kg DEX at the start of surgery lowered the incidence of AKI and serum level of renal biomarkers like BUN, creatinine, and cystatin C.[60]

Table 1: Summary of published meta-analyses on the effect of dexmedetomidine on acute kidney injury.

Study	Patient population	N	Studies included	Primary outcome	Main results
Peng et al.[53] 2020	Adult cardiac surgery	1,308	9 RCTs	Incidence of AKI	DEX reduced incidence of AKI (RR: 0.60; 95% CI: 0.41–0.87; p=0.008)
Liu et al.[54] 2018	Adult cardiac surgery	1,575	10 RCTs	Incidence of AKI within 7 days	DEX reduced incidence of AKI (OR: 0.65; 95% CI: 0.45–0.92; p=0.02)
Shi and Tie[55] 2017	Adult cardiac surgery	19,266	3 RCTs 4 observational	Incidence of AKI	DEX reduced incidence of AKI in the RCTs (RR: 0.44; 95% CI: 0.26–0.76; p=0.003) and cohort studies (RR: 0.74; 95% CI: 0.63–0.86; p=0.0001)
Li et al.[56] 2018	Paediatric cardiac surgery	1,851	5 RCTs 4 observational	Postoperative junctional ectopic tachycardia and AKI	No difference in AKI (OR: 0.44; 95% CI: 0.19–1.04; p=0.06) AKI reported in 73/233 patients (31.3%) among one RCT and one observational study

AKI: acute kidney injury; CI: confidence interval; DEX: dexmedetomidine; N: number of patients; OR: odds ratio; RCT: randomised controlled trial; RR: risk ratio.

Table 2: Characteristics of relevant studies on the effect of dexmedetomidine on acute kidney injury in non-cardiac surgery patients.

Reference	Study design	Patient population	N	Blinding	Dose	Timing	Control group	Primary outcome	Main results
Kawazoe et al.[20] 2017	RCT	Sepsis and mechanical ventilation for >24 hours	201	No	0.1–0.7 µg/kg/hour IV	After 24 hours	Propofol/ midazolam	Mortality and ventilator-free days at Day 28	No difference in (secondary) renal outcomes (urinary output, creatinine, eGFR, BUN)

Table 2 continued.

Reference	Study design	Patient population	N	Blinding	Dose	Timing	Control group	Primary outcome	Main results
Liu et al.[78] 2015	RCT	Septic shock and mechanical ventilation	200	NR	1 µg/kg bolus, then 0.2–0.3 µg/kg/hour IV	From ICU admission until Day 5	Propofol	NR	Incidence of AKI 38.1% in the DEX group versus 59.6% in controls (OR: 0.76; 95% CI: 0.13–0.77; p=0.046)
Wu et al.[60] 2019	RCT	Laparoscopic radical prostatectomy	89	Double-blind	1 µg/kg bolus, then 0.5 µg/kg/hour IV	During surgery	0.9% NaCl	Incidence of AKI	AKI in the DEX group 2/44 (4.5%) versus 6/45 (13.3%) in controls (p=0.281).
Zhang et al.[61] 2019	RCT	Pre-eclampsia undergoing caesarean section	134	Double-blind	Intrathecal: 0.6–0.4 µg/kg/min IV: 0.4 µg/kg/min	During/before surgery	0.9% NaCl	NR	β2-MG, KIM-1, and urine protein lower in the DEX group. No significant difference in BUN, creatinine, or urine output.
Moon et al.[85] 2002	Retrospective observational	Elective lung cancer surgery	1,207	NA	0.2–0.7 µg/kg/hour	NR	No DEX	Incidence of AKI	Incidence of AKI 7% in the DEX group versus 8.4% in controls (p=0.45)

AKI: acute kidney injury; BUN: blood urea nitrogen; β2-MG: β2-microglobulin; CI: confidence interval; DEX: dexmedetomidine; eGFR: estimated glomerular filtration rate; ICU: intensive care unit; IV: intravenous; KIM-1: kidney injury molecule-1; N: number of patients; NA: not applicable; NaCl: sodium chloride; NR: not reported; OR: odds ratio; RCT: randomised controlled trial.

However, this was a small, underpowered pilot study and the overall incidence of AKI was low (4.5% in the DEX group and 13.3% in the control group), thus increasing the risk of a Type-I error. In a recent double-blind placebo-controlled RCT in 134 women undergoing caesarean section for pre-eclampsia, intravenous DEX (0.4 µg/kg/min for 10 minutes before surgery) resulted in lower β2-microglobulin, kidney injury molecule-1, and urine protein, but not in significant

differences in BUN, serum creatinine, or urine output.[61]

DEXMEDETOMIDINE FOR THE PREVENTION OF ACUTE KIDNEY INJURY IN SEPSIS

AKI occurs in up to 50% of patients with sepsis, one-third of whom do not survive.[64] Although sepsis is the most common cause of severe AKI in patients in the ICU, the exact mechanisms are still under investigation.[65] An increased level of inflammatory cytokines and leukocyte activity can lead to the capillary microthrombi resulting in microvascular dysfunction. Redistribution of intrarenal blood flow due to abnormal vascular tone and shunting, renal inflammation, and oedema can decrease capillary perfusion and oxygen delivery. Sepsis-induced hypotension in addition to the microcirculatory dysfunction can further impair perfusion and oxygen delivery to the kidneys due to renal medullary tissue hypoperfusion and hypoxia.[66,67] Early onset of renal medullary hypoxia and tissue ischaemia occurs hours before the development of AKI, despite elevated or unchanged renal blood flow, renal oxygen delivery, and renal cortical perfusion and oxygenation.[68-70]

The reno-protective effects of DEX in animal models have been related to its anti-inflammatory properties, which can attenuate sepsis-induced microcirculatory dysfunction.[71] Both clonidine and DEX reduce the levels of pro-inflammatory cytokines (TNF-α and IL-6), while preserving the levels of an anti-inflammatory cytokine (IL-10) in septic sheep with AKI.[72,73] In rodent models, DEX protects against AKI, although treatment was given either intraperitoneally[35,72-74] or prior to sepsis.[38,77-79] A single-centre clinical trial in 200 patients with sepsis found reductions in plasma inflammatory cytokines (TNF-α and IL-1), serum creatinine, and urinary injury biomarkers in patients receiving DEX (1 µg/kg bolus at ICU admission, and then 0.2–0.3 µg/kg/hour for 5 days) compared with propofol.[62] However, the findings of this trial must be interpreted with caution as the primary outcome was not clearly defined, no sample size calculation was provided, the study protocol was not published a priori, and blinding and randomisation were not described.

In agreement with experimental findings, renal medullary tissue hypoxia has recently been indirectly demonstrated in humans with sepsis by measurable declines in bladder urinary oxygenation.[81] Administration of noradrenaline can aggravate renal medullary ischaemia and hypoxia.[68,69,82] In patients with sepsis, co-administration of DEX reduces noradrenaline requirements to attain the target blood pressure,[83] an effect associated with preservation of renal medullary perfusion, renal medullary oxygenation, and kidney function.[73] In the Dexmedetomidine for Sepsis in Intensive Care Unit (DESIRE) trial (N=201 patients) DEX did not significantly affect renal outcomes or 28-day mortality.[20] However, a recent sub-group analysis of 104 patients with severe sepsis (Acute Physiology and Chronic Evaluation II scores of ≥23) found lower serum creatinine levels, improvements in renal Sequential Organ Failure Assessment (SOFA) sub-scores, and a decrease in 28-day mortality (22% versus 42%) in the DEX group.[84]

Despite the current lack of convincing clinical evidence to prove the renal benefits of DEX in patients with sepsis, data from animal studies support strategies that protect the kidneys from I-R injury.[85] Although it is conceivable that DEX provides a protective effect in the evolution of AKI, its effect on long-term outcomes remains unknown. In a rat model, Liu et al.[42] demonstrated that DEX improved histological signs of renal injury up to 8 weeks after renal clamping. However, most randomised clinical trials found either only a transient effect on renal parameters or provided only short-term follow up in the range of a couple of days. The DESIRE trial[20] showed no difference in AKI, a secondary outcome, after 28 days and the above-mentioned sub-group analysis by Nakashima et al.[84] found significantly lower serum creatinine but no difference in urinary output in the first 14 days.

CONCLUSIONS AND FUTURE DIRECTIONS

Numerous animal studies suggest a reno-protective effect of DEX after a controlled insult such as I-R injury or experimental sepsis. These effects are more reproducible with

intraperitoneal injection of DEX, compared to the more clinically relevant intravenous route. In clinical practice, three meta-analyses confirm a beneficial effect of DEX on renal function in patients after cardiac surgery. However, the evidence for similar benefits in patients with sepsis or in non-cardiac surgery is less convincing. An important difference between these trials is the timing of DEX administration relative to the noxious insult. While in cardiac surgery the onset of CPB is predictable, it is impossible to predict the exact time of onset of sepsis, massive blood loss, or hypotension. Importantly, due to its sympatholytic properties, DEX may aggravate haemodynamic instability, raising concern for additional renal hypoperfusion with its use. However, in their systematic review, Peng et al.[53] did not find any differences in hypotension or bradycardia or the need for vasopressors with DEX use, and, in patients with sepsis, DEX may actually decrease vasopressor requirements.[83] Moreover, a high inter-individual variability in DEX pharmacokinetics has been described, especially in patients in the ICU and body size, liver function, plasma albumin, and cardiac output all have a significant impact on DEX pharmacokinetics.[5] As outlined above, any baseline variability regarding these factors among trial participants must be considered when interpreting the results of clinical trials.

The assessment of the incidence of AKI in different patient populations has been complicated by the various definitions for AKI used over time.[85] The challenges in applying diagnostic criteria in the critically ill patient are considerable. If the true baseline creatinine level is not available and a 'baseline' creatinine level is obtained only after a significant amount of intravenous fluid has been administered, AKI diagnosis may be falsely common because the 'baseline' creatinine value may be falsely low due to haemodilution is these settings.[86] Moreover, ongoing fluid administration can decrease serum creatinine concentration and thereby conceal loss of GFR in such patients. Finally, the widespread use of diuretics and intravenous fluids in the perioperative period may render urine output an unreliable indicator of true renal function. Future trials are needed to determine the dose and timing of DEX in improving outcomes in different patient populations, especially in patients with decreased baseline kidney function.

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Causes of Hypermagnesaemia: A Literature Review

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Abstract

Magnesium is one of the commonly overlooked electrolytes, yet it plays a vital role in many of the processes in the human body. The balance of magnesium can translate into subtle changes in a person's daily life, causing fatigue and confusion, to extreme cases that can end up causing central nervous system depression, respiratory failure, or cardiac arrhythmias.

It is vital to be familiar with the physiology of magnesium regulation and knowledgeable regarding the causes that can lead to its toxicity to ensure the prevention of the possibly fatal condition.

Magnesium balance can be summarised as the difference between magnesium intake and its excretion. Any factor overwhelming either of the two factors can cause pathological levels of the electrolyte. In addition to learning preventive measures to help patients against effects of magnesium toxicity, it is also important that the medical community trains to be able to treat cases of hypermagnesaemia.

This review assesses the latest advancements in knowledge of magnesium metabolism, examines the case reports of hypermagnesaemia in an attempt to list the causes of magnesium toxicity, and enumerates management advances for the condition.

INTRODUCTION

Magnesium is a chemical element with an atomic number of 12. It is among the top 10 most abundant elements in nature. In the human body, it is the second most prevalent cation intracellularly and the fourth most common cation extracellularly.[1] The body contains approximately 24–26 g (1,000 mmol) of magnesium.

Magnesium plays a fundamental role in the body's metabolic processes and is involved in more than 300 enzymatic reactions.[2-5] It serves as a cofactor in ATPase–phosphate transfer reactions,[4,6] oxidative phosphorylation processes,[7-9] and synthesis of nucleic acids.[10,11] It also actively contributes to glycolysis[12,13] and lipid and protein metabolism,[14] and affects intracellular signalling and cell membrane stabilisation.[15]

Magnesium is crucial in balancing the effects of calcium in the body and acts by inhibiting calcium-mediated smooth muscle contraction.[16,17] This translates into vasodilatory properties and is important for blood pressure maintenance. Magnesium antagonism of calcium is also integral in the nervous tissues, where calcium helps

maintain the resting membrane potential. Excess magnesium levels lead to hyperpolarisation of the nervous tissues, indirectly inhibiting acetylcholine receptors and N-methyl-D-aspartate receptor-mediated central nervous system conductivity, resulting in central nervous system depression.[18]

PHYSIOLOGY OF MAGNESIUM

Sixty percent of the magnesium in the body is stored in the bones. The remainder is distributed between the intracellular compartment of the muscles and soft tissues, with only 1% found in the extracellular compartment.[19,23] Ionised magnesium constitutes 64% of the extracellular magnesium. The remainder is attached to albumin and other anions in the blood.[19] Magnesium is referred to as the 'orphan electrolyte' due to its lack of specific endocrine control. Thus, serum magnesium levels are consistently maintained by a strict balance between intestinal absorption, renal excretion, and bone buffering of magnesium. The skeletal system has the ability to provide 30% of its magnesium stores in settings of hypomagnesaemia.[24]

Magnesium Intake

Diet is the primary source of magnesium for the body; the latter half of the small intestine contributes to approximately 80% of the dietary magnesium absorption,[25] and the rest occurs in the proximal small intestine and the colon (Figure 1). The majority of intestinal magnesium absorption occurs through the paracellular pathway and is driven by electrochemical gradients.[26,27] Transcellular absorption also occurs via transient receptor potential channel subfamily M (TRPM) member 6 (TRPM6),[28] possibly via TRPM7,[29] and through magnesium–anion complex channels.[30] The absorption of magnesium from enterocytes to the bloodstream is facilitated by the sodium/magnesium-ATPase, which is found on the basolateral side of the intestinal cells and uptakes a plasma sodium ion into the enterocyte in exchange for a magnesium ion absorbed into the plasma. The intracellular sodium gradient is balanced by sodium/potassium-ATPase (Na^+/K^+-ATPase) on the basolateral side, which pumps the sodium ions back into the plasma from the intestinal cells, making them available again for the sodium/magnesium exchanger. This sodium exchange, assisted by concentrations of chloride ions, bicarbonate ions, and fatty acids, ensures an electrochemical gradient favouring magnesium uptake into the intestinal cells and then the plasma.

Depending on the magnesium levels, the intestine can absorb 11–65% of oral magnesium content.[24] Despite the lack of a specific endocrine control, magnesium is regulated by multiple factors such as parathyroid hormone, thyroid hormone, growth hormone, vitamin D, and dietary sodium content.[31] The intestinal mobility and intestinal epithelial health also play a vital role in magnesium homeostasis. Changes in the intestinal transit time and the intestinal blood supply directly correlate with serum magnesium levels. The daily recommended dose of magnesium is 4.5 mg/kg[24] and up to 350 mg.[32] Magnesium is abundant in dairy products, fruits, vegetables, fish, meat, legumes, and nuts.

Magnesium Elimination

Active magnesium excretion is fundamental in preventing magnesium accumulation. In the body this is mediated by only two organ systems: the kidneys and the skin (via sweating). Even though the intestinal tract does not have an active role in plasma magnesium excretion, it can waste the surplus dietary magnesium by downregulating the intestinal absorption based on serum magnesium levels.[33] The kidneys play a pivotal role in maintaining an optimal magnesium concentration in the body. Since 20% of the serum magnesium is albumin bound, a healthy kidney filters 80% of serum magnesium and usually reabsorbs 95% from the filtrate. However, in magnesium-depleted states, the kidneys can increase this reabsorption capacity to 99.5%.[34] On the other hand, the kidneys usually excrete approximately 100 mg of magnesium per day in the urine but have the ability to excrete up to 70% of the filtered magnesium (Figure 1).

Renal handling of magnesium differs from other electrolytes in that the predominant site of tubular reabsorption is the thick ascending limb (TAL) loop of Henle rather than the proximal convoluted tubule. Indeed, the TAL reabsorbs 70% of the filtered magnesium while approximately 15% is reabsorbed in each of the proximal convoluted tubule and distal convoluted tubule (DCT) (Figure 2).

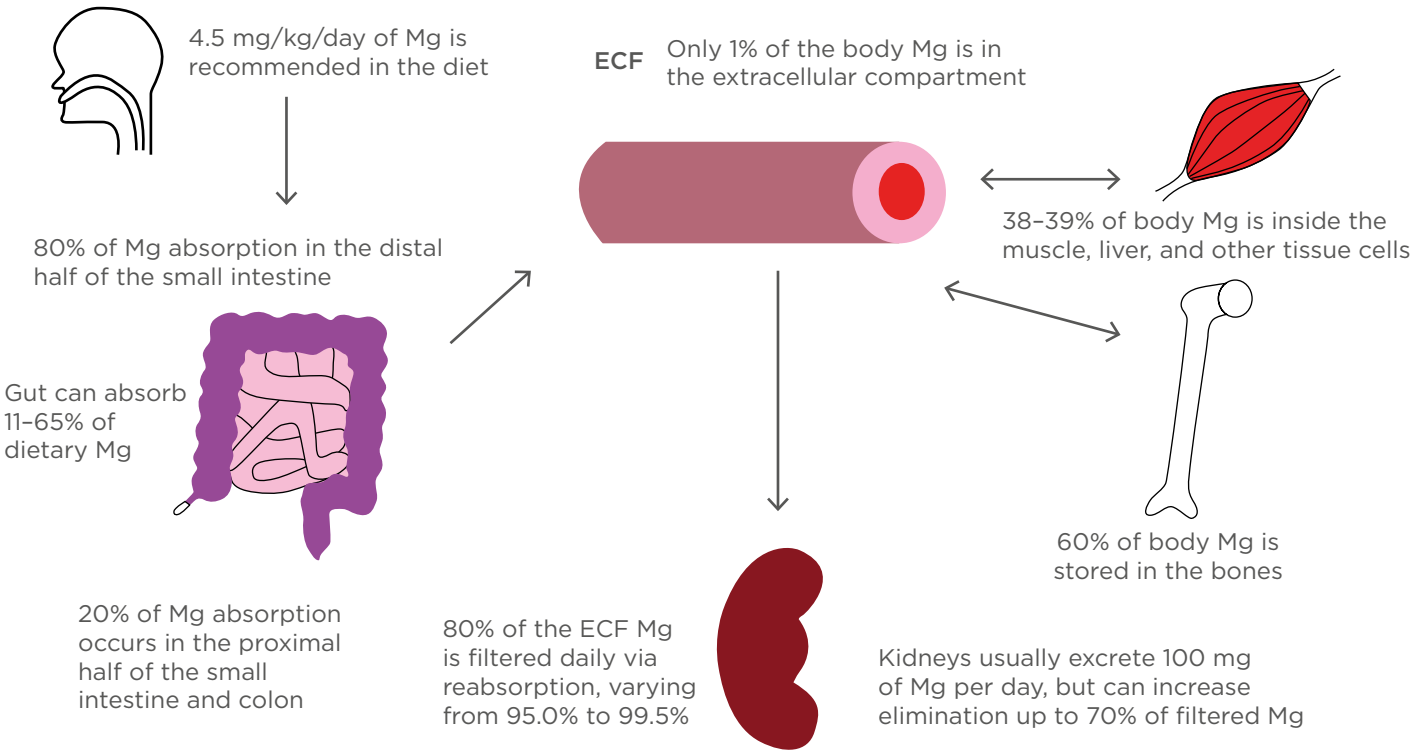

Figure 1: Absorption and distribution of magnesium.

All Mg intake is usually by mouth. 4.5 mg/kg/day of dietary magnesium is recommended. Eighty percent of dietary Mg is absorbed in the later half of the small intestine and the remainder in the rest of the small and large intestine. The gut can vary in the absorption of dietary magnesium content (11–65%). Of the 24–26 g Mg in the body, 60% is in the bones, 38–39% in the liver and muscle tissue, and 1% is in the extracellular compartment. Kidneys usually filter 80% of serum magnesium per day and can vary reabsorption from 95.0–99.5% of the filtrate. Urine Mg content can vary from 0.1 to >1.0 g/day.

ECF: extracellular fluid; Mg: magnesium.

Most of the reabsorption in the TAL occurs through paracellular transport with assistance from paracellin-1 membrane proteins, mediated by the electrochemical gradient between the tubular lumen and interstitium. This gradient is established in the TAL by maintaining a net-positive gradient of +8 mV (positive charge) in the tubular lumen via potassium excretion back into the tubule via the renal outer medullary potassium channel (ROMK), after initial potassium influx by sodium-potassium-2 chloride cotransporter (NKCC2).

By regulating and fine-tuning the magnesium reabsorption at the very end, the DCT regulates the amount of magnesium in the urine and is thus a key determinant of magnesium excretion.[34,35] In the DCT, transcellular reabsorption plays a key role. This is brought about by the TRPM6 and is influenced by calcineurin (by affecting NaCl cotransporter expression).[35] Other channels that contribute to the electrochemical gradient in the DCT include the Na^+/K^+-ATPase voltage-gated chloride channels on the basolateral side and the voltage-gated potassium channels on the luminal side. These channels collaborate to promote potassium excretion into the lumen to maintain a relatively positive charge in the lumen, helping absorb magnesium (Figure 2). Notably, factors increasing the Na^+/K^+-ATPase or voltage-gated potassium channel activity such as the renin–aldosterone system can promote magnesium reabsorption.[35,36] Being the orphan electrolyte of the body, magnesium reabsorption is modestly influenced by multiple hormones including insulin, parathyroid hormone, antidiuretic hormone, glucagon, renin, aldosterone, and calcitonin.[1,24,37] Local prostaglandins, hypercalcaemia, and diuretics have also been noted to affect renal magnesium reabsorption in the tubules.[37]

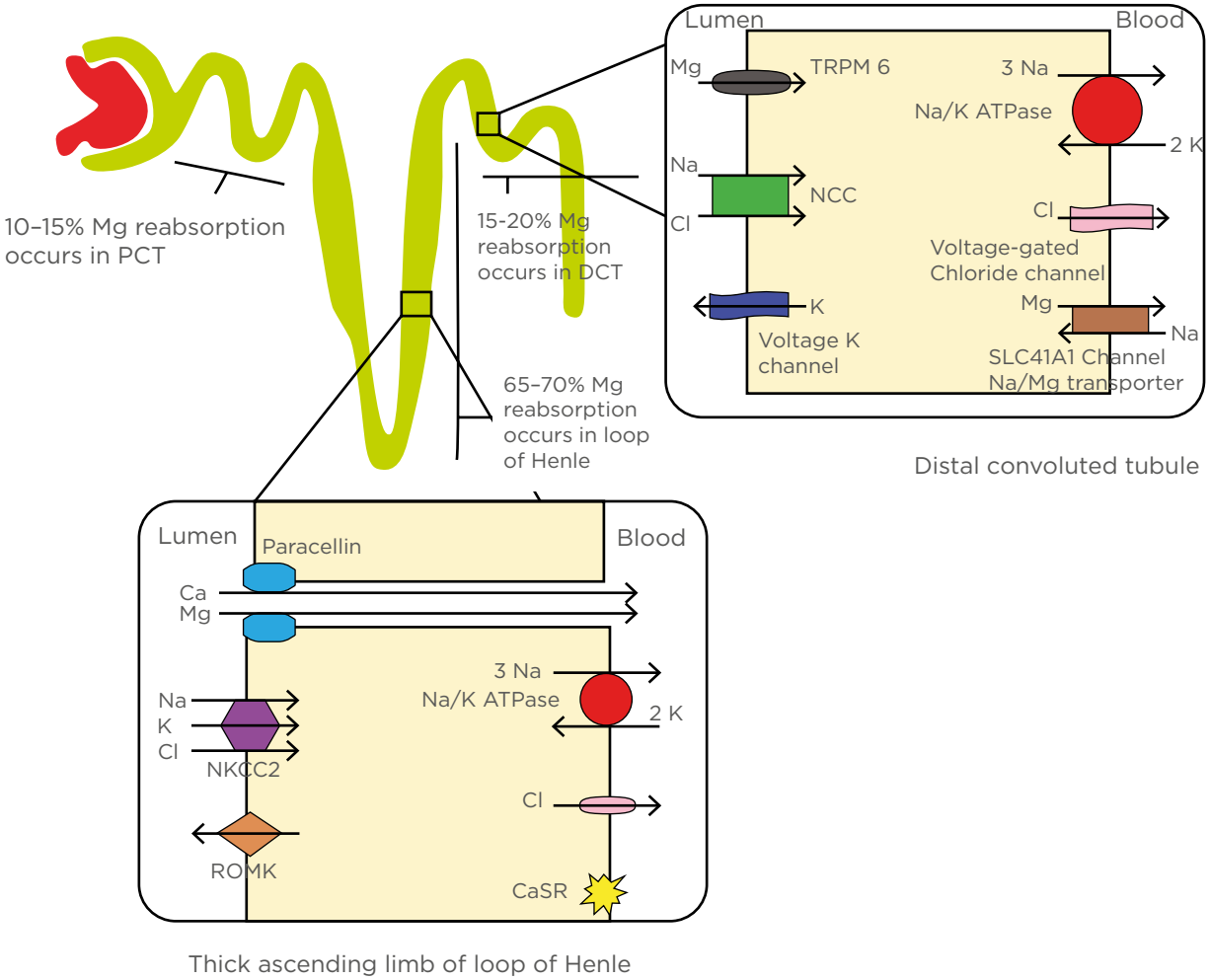

Figure 2: Renal handling of magnesium.

Mg reabsorption occurs 60–70% in the loop of Henle, 10–15% in the PCT, and 15–20% in the DCT. In the loop of Henle, the NKCC2, the renal outer medullary K channel on the luminal side, and Na^+/K^+-ATPase on the basolateral side maintain a positive gradient in the lumen by secreting K into the channel. This helps create an electrochemical gradient between the lumen and the blood, forcing Ca and Mg reabsorption through paracellular movement. The CaSR on the basolateral side of the loop of Henle cells also influences activity of NA^+/K^+-ATPase and the NKCC2, which inhibits their activity and controls the electrochemical gradient. In the DCT, Mg reabsorption occurs through the TRPM6 and TRPM7 on the luminal side and the SLC41A1 protein at the basolateral side, which is proposed to act as a Na/Mg counter-transporter. Voltage-gated K channel-guided potassium secretion, the NCC at the luminal side, and voltage-gated Cl channels help control the flow of Mg ions.

Ca: calcium; CaSR: calcium-sensing receptor; Cl: chloride; DCT: distal convoluted tubule; K: potassium; Mg: magnesium; Na: sodium; NCC: sodium chloride cotransporter; NKCC2: sodium-potassium-2 chloride cotransporter; PCT: proximal convoluted tubule; ROMK: renal outer medullary potassium channel; SLC41A1: solute carrier family 41 A1; TRPM6: transient receptor potential channel subfamily M member 6.

HYPERMAGNESAEMIA

Epidemiology

Normal magnesium levels vary from 0.7–1.0 mmol/L or 1.7–2.4 mg/dL.[31] Hypermagnesaemia is thus defined as magnesium levels equal to or greater than 1.1 mmol/L or 2.5 mg/dL. Levels greater than 2.0 mmol/L or 4.7mg/dL are considered critical. The incidence of hypermagnesaemia in hospitalised patients varies based on the study, from 3–5%[38] and up to 10–12%.[39,40] Incidence is higher in patients with suboptimal kidney function[41] and in patients in the intensive care unit.[40]

Consequences of Hypermagnesaemia

Magnesium toxicity can range from an asymptomatic laboratory abnormality to widespread and sometimes fatal manifestations. The most common systems affected by magnesium toxicity are the nervous, cardiac, respiratory, and gastrointestinal systems. In mild cases, presentation might only involve nausea, light-headedness, and confusion. As magnesium levels rise above 7 mg/dL, the symptoms can become more serious with worsening drowsiness, decrease in deep tendon reflexes, blurring of vision from impaired pupillary accommodation, ileus, and bladder paralysis. It can also affect the cardiovascular system, causing hypotension and bradycardia. When magnesium levels rise higher than 12 mg/dL, life-threatening conditions ensue, including flaccid paralysis, respiratory depression, and cardiac arrhythmias, notably bradycardia and prolongation of the PR interval. This progresses to encompass fatal events with cardiorespiratory arrest or coma at magnesium levels ≥15 mg/dL.[31]

Hypermagnesaemia is associated with increased mortality. In a recent study of >14,000 patients, it was noted that the 30-day all-cause mortality was twice as high in patients with hypermagnesaemia compared to patients with normal serum magnesium levels.[39]

Causes of Hypermagnesaemia

The human body is well equipped to handle high loads of magnesium. Between bone magnesium buffering, controlled intestinal absorption, and, most importantly, the renal ability to precisely reabsorb only the required levels of magnesium, it is uncommon to find life-threatening hypermagnesaemia. To have hypermagnesaemia, intake must exceed excretory ability; thus, most cases of hypermagnesaemia occur in a situation of decreased kidney function with the inability, therefore, to excrete extra magnesium.[42]

Kidney disease

Kidney dysfunction, both acute and chronic, is possibly the most common cause of hypermagnesaemia. This is usually compounded by an increased magnesium intake. In one study, over 70% of patients with hypermagnesaemia had an underlying decrease in glomerular filtration rate (GFR).[42] In a recent case series, 85% of patients with hypermagnesaemia had chronic kidney disease (CKD) and only 15% had normal creatinine levels.[43] Factors that can decrease renal filtration of magnesium, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, non-steroidal anti-inflammatory drugs, adrenal insufficiency,[24,31] hypothyroidism,[24,31] and even hyperkalaemia (by causing bradycardia and hypotension in extreme cases), can cause worsening magnesium toxicity.[20,35,44] Many cases of hypermagnesaemia occur in elderly patients with CKD on concomitant medications, like those mentioned above. Magnesium toxicity has been documented repeatedly in patients on lithium. The exact mechanism is unknown, but it is suspected to be driven by lithium-induced hypovolaemic state with a subsequent increase in renin and aldosterone stimulation leading to the increase in magnesium retention.[24,31,45]

Iatrogenic

The second most common cause of hypermagnesaemia is aggressive replacement or therapeutic usage of magnesium compounds. This is mostly seen in patients receiving intravenous magnesium infusions, such as obstetrics patients with pre-eclampsia or eclampsia.[31] Hypermagnesaemia in these cases usually occurs despite normal kidney function since the rate of infusion exceeds the rate of renal excretion. Newborn infants of such patients have also been reported to have iatrogenic magnesium toxicity at birth, while some pre-term infants whose mothers were on magnesium-containing parenteral nutrition have also been reported to have symptomatic hypermagnesaemia. Magnesium-based bowel preparation regimens are some other commonly described iatrogenic causes of hypermagnesaemia.

Excessive absorption

Magnesium toxicity from increased intestinal absorption can occur either by surplus intake or prolonged intestinal exposure to the ingested magnesium content. Most cases of hypermagnesaemia, regardless of renal function, have exposure to exogenous magnesium in the form of magnesium-containing supplements, laxatives, antacids, cathartics, or enemas.[44,46] Magnesium oxide, a commonly used laxative, is notorious for cases of toxicity in the elderly.[43]

The oral bioavailability of magnesium can vary from approximately 15% to 60%[47] based on the ingested daily magnesium content. Magnesium oxide doses >1 g/day have been noted to increase risk of toxicity.[48] Increased intestinal magnesium absorption can also be due to increased surface contact time between the magnesium and the intestinal cells, by a richer blood supply to the intestine, or decreased intestinal transit time. Thus, inflammatory bowel disease (through increased enteric blood supply) and constipation or ileus (through slower transit) can lead to hypermagnesaemia, regardless of the dietary magnesium content or normal kidney function. Both conditions lead to a vicious cycle, with increased magnesium levels slowing peristalsis and resulting in worsening ileus and increased intestinal absorption of magnesium.[46,49] Medications causing constipation such as opiates and anticholinergics can precipitate hypermagnesaemia in the same manner.[24] Vitamin D and its analogues cause increased magnesium absorption in the intestine and when coupled with CKD have resulted in cases of hypermagnesaemia.[35,43]

Rare causes

Magnesium toxicity has also been reported in cases of haemolysis, tumour lysis, rhabdomyolysis, and metabolic acidosis due to extracellular shifts of the intracellular magnesium stores. Sepsis, intestinal perforation, and intestinal ischaemia are some of the other uncommon conditions where hypermagnesaemia has been noted.[35] Urethral irrigation with magnesium-rich hemiacidrin,[24] which is used in nephrolithiasis management, has also been documented with cases of magnesium toxicity. Epsom salts (rich in magnesium) being used as laxatives have been reported as causes of hypermagnesaemia that require emergent hospitalisations.[50,51] Calcium-alkali syndrome[31] and familial hypocalciuric hypercalcaemia[35,52] can result in magnesium toxicity because of decreased renal magnesium excretion. In familial hypocalciuric hypercalcaemia, there is an inactivating mutation in the calcium-sensing receptor gene (*CaSR*). This receptor is usually present in all segments of the kidney but most abundant on the basolateral side of the TAL. The CaSR usually regulates sodium chloride and divalent cation transportation both paracellularly and transcellularly; it does so by influencing multiple channels including NKCC2 and ROMK (normally inhibiting their activity in hypercalcaemic conditions) to help maintain a specific electrochemical gradient.[53] An inactivating mutation of the CaSR causes hyperactivity of NKCC2 and ROMK and increases the positive charge in the lumen; this indirectly enhances paracellin activity, which eventually drives divalent cation transportation across the tubular cells and results in higher calcium and magnesium reabsorption both transcellularly and paracellularly.[53] Calcium-alkali syndrome can also present as hypermagnesaemia caused by multiple indirect factors including magnesium-containing antacids, decreased intravascular volume, and acute kidney injury, all contributing to increased magnesium retention.[54] Other rare causes include calcitriol (by increasing intestinal magnesium absorption)[1] and ingestion of salt water[55] from the Dead Sea, Western Asia (which has a high magnesium content). Conditions involving increased aldosterone, with or without increased renin levels, have also been linked with hypermagnesaemia. This happens due to aldosterone-mediated hyperactivity of Na^+/K^+-ATPase, ROMK, the sodium–chloride cotransporter, and voltage-gated potassium channels (in DCT), resulting in a higher positive charge in the tubular lumen and causing magnesium flow towards the basolateral side due to an increased electrochemical gradient.[35,36] The causes of hypermagnesaemia are summarised in Table 1.

MANAGEMENT

Most of the cases of hypermagnesaemia are asymptomatic to mildly symptomatic, yet an increased mortality rate has been noted in patients with hypermagnesaemia who are admitted to the hospital. Identifying and removing the culprit agent is the foremost step to the management of hypermagnesaemia. Asymptomatic cases with a normal GFR do not require specific treatment, except from withholding all magnesium-containing medications; thereby, excess magnesium is usually excreted in the urine. The half-life of magnesium in the body with a functioning kidney is approximately 28 hours.

Table 1: Causes of hypermagnesaemia.

Decreased renal excretion
Acute or chronic kidney disease, dialysis dependence
Hyperkalaemia
Medications (diuretics, ACEi/ARB, NSAID, PPI, lithium, vitamin D supplements)
Hyperreninaemia, hyperaldosteronism
Hypothyroidism
Adrenal insufficiency
Calcium-alkali syndrome
Familial hypocalciuric hypercalcaemia
Increased intake
Iatrogenic (IV infusions, magnesium-based bowel preparation)
Neonates born to mothers on IV magnesium
Magnesium supplements
Magnesium-based laxatives, cathartics, gargles, antacids, enemas
Hemiacidrin (urethral irrigation)
Decreased intestinal transit time
Constipation, ileus
Medications causing decreased GI motility (opioids, anticholinergics)
Relative increased intestinal vascular flow
Inflammatory bowel disease
Increased cellular shifts
Haemolysis, tumour lysis, rhabdomyolysis
Metabolic acidosis

ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; GI: gastrointestinal; IV: intravenous; NSAID: non-steroidal anti-inflammatory drugs; PPI: proton-pump inhibitors.

In settings of acute symptomatic toxicity, it is essential to rapidly lower magnesium levels. Medical management is usually also required in patients with hypermagnesaemia with CKD and estimated GFR (eGFR) between 15 and 45 mL/min/1.73m^2. The foremost step is to administer a dose of 100–200 mg of elemental calcium over 5–10 min to rapidly counteract the neuromuscular and cardiovascular ramifications of hypermagnesaemia. This can be achieved by administering either calcium chloride or calcium gluconate intravenously. Magnesium renal excretion can be augmented with the help of loop diuretics, such as furosemide at a dose of 1 mg/kg. This dose can be increased depending on eGFR. Magnesium excretion with diuretics is further aided by adding intravenous isotonic fluids, such as saline at 150 mL/hour.

Dialysis is indicated in cases of severe (levels >6 mg/dL), symptomatic hypermagnesaemia, where patients have critical symptoms or anuria. Patients with an eGFR usually <15 mL/min/1.73m^2 and hypermagnesaemia also often require treatment with dialysis. In such cases, medical management should be started immediately while dialysis is being established. Haemodialysis is preferred over peritoneal dialysis because it reduces magnesium levels faster; haemodialysis can be expected to remove 50% of the magnesium load in a 4-hour session.[31]

CONCLUSION

Magnesium is one of the most important electrolytes in the body. While justified emphasis is given to hypomagnesaemia and its role in cardiac arrhythmias, hypermagnesaemia can have equally debilitating effects. Hypermagnesaemia can have widespread effects in the body and affects the nervous, cardiovascular, respiratory, and gastrointestinal systems. It can be a cause of altered mentation, ranging from somnolence to coma, and other fatal conditions, ranging from respiratory failure to cardiac arrhythmias. Often, magnesium toxicity is the result of the co-administration of multiple medications, which individually might be safe but when given together, especially in patients with predisposing conditions like kidney disease, can result in adverse events. It is not only prudent to identify the signs and symptoms of magnesium toxicity early and reverse the disorder, but equally valuable to be familiar with the causes of hypermagnesaemia. Distinguishing the magnesium-rich medications or those with the potential to cause an increase in magnesium absorption or decrease in magnesium excretion must be a part of daily medical practice; this is imperative to prevent harm occurring to the predisposed patient population at high risk of developing magnesium toxicity.

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