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NEPHROLOGY

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"For those who attended and are looking to refresh their memory, or for those who were unable to attend, we have consolidated all the best bits from ERA-EDTA 2019 in our Congress Review."

Spencer Gore, CEO

Editorial Board

VIEW IN FULL ←

Aims and Scope

The European Medical Journal (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: Budapest, Hungary home of the ERA-EDTA 2019. © Tomas Marek / 123rf.com

EMJ Nephrol.

Welcome

Welcome to the latest edition of *EMJ Nephrology*; this journal is packed with updates and developments from the exciting field of nephrology. Not only does this edition contain excellent peer-reviewed articles, but also highlights from the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) congress, which was brimming with attendees full of energy and the enthusiasm to share knowledge.

Along with thousands of other nephrology experts, we attended this year's ERA-EDTA congress held in the stunning city of Budapest, Hungary. If you were fortunate enough to attend, then you are already aware of some of the ground-breaking work that was delivered to a wonderfully diverse audience.

For those who attended and are looking to refresh their memory, or for those who were unable to attend, we have consolidated all the best bits from ERA-EDTA 2019 in our Congress Review. Abstract summaries, written by the presenting authors themselves, discuss the hottest topics in nephrology, reflecting the impressive range of research presented at ERA-EDTA. With some drawing attention to considerations that need to be taken during haemodialysis treatment, these abstracts will surely improve aspects of your day-to-day practice. Haemodialysis is always a prevalent topic at congress, and this year was no exception. Excitingly, Kotanko et al. presented a novel and unique solution to the shortage in renal replacement therapy in an evolution of the standard haemodialysis; it's a must-read abstract summary.

The key phrase chosen for this year's congress was 'precision nephrology'; aiming to provide the best care for patients, precision nephrology paves the way to patient and disease-focussed pharmaceuticals and treatments. This focus sparked an abundance of discussion at congress, providing ideas on how to tackle some of the most difficult challenges facing nephrologists and patients today.

In addition to the ERA-EDTA congress review, *EMJ Nephrology 7.1* also offers a brilliant collection of peer-reviewed articles covering the latest discoveries. The theme of new kidney disease approaches and interventions continues in the articles, including interventions to prevent infections in dialysis catheters and the use of stem cells to bridge the gap between the high need and limited availability of renal replacement therapy.

I would like to finish by thanking everyone who worked so hard to produce such an amazing edition of our nephrology journal. As always, we are so proud and thrilled to be able to contribute to such a patient care-orientated field and look forward to working with many more authors in the future.

Spencer Gore

Chief Executive Officer, European Medical Group

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Foreword

Dear colleagues,

It is a pleasure to welcome you to this year's edition of *EMJ Nephrology*, a journal full of updates from, and for, the nephrology community. From excellent peer-reviewed articles, to interviews with key opinion leaders, you will undoubtedly find something of interest to read.

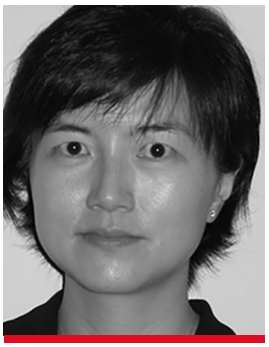
As seen in many therapeutic areas, stem cells are paving the way to novel approaches in treating and modelling diseases and nephrology is not an exception. With the shortage of kidneys for transplantation a never-ending challenge, an alternative long-term treatment that can be rolled out to the masses of patients in need is of utmost importance. My Editor's Pick for this edition, the article by Morizane et al., provides a summary of the current status of stem cell-based treatments for kidney disease, highlighting the great potential the treatment option has. This illuminating review delivers an in-depth analysis of the different stem cell types that can be utilised, and how they can be manipulated, inclusive of the potential of xenotransplantation in regenerative medicine.

While newer technologies and treatments are being developed, many with kidney disease are still reliant on haemodialysis. Although this life-saving treatment is absolutely necessary, it does present with risks and complications that can be fatal, including microbial infections of venous catheters that lead to sepsis. A literature meta-analysis by Ponce et al. reviews prophylactic antimicrobial therapy that can be used to reduce the occurrence of microbial infections in those who use haemodialysis. Not only does this comprehensive article cover topical and systemic antimicrobials, but also antimicrobial lock therapy, a technology that has been hotly debated within the nephrology community.

Complimentary to this discussion, multiple abstract summaries that were presented at ERA-EDTA 2019, held in Budapest, Hungary, this year can be found in the congress review. Highlighting new research in haemodialysis and other important topics, these abstracts are a great method to keep up to date with cutting-edge research. Prof György Reusz, president of the Hungarian Society of Nephrology and congress co-president of ERA-EDTA, was kind enough to answer EMJ's questions in an interview with them. Providing an insight into the congress and its associated scientific programme, the interview is a great addition to this year's congress review, and definitely not one to miss.

I am sure you will find this issue of *EMJ Nephrology 7.1* both informative and entertaining, as well as applicable to your daily practice.

Best wishes,



Dr Angela Yee-Moon Wang

University of Hong Kong, Queen Mary Hospital, Hong Kong

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Congress Review

+ Review of the 34th European Association of Urology's (EAU) Annual Meeting Barcelona, Spain, 15th–19th March 2019

Congress Feature

+ The Nightmare Stones Session

Congress Interview

+ Prof Dr Hendrick Van Poppel

Abstract Reviews

Articles

+ Editor's Pick: The Efficacy and Safety of Flexible Ureterorenoscopy in Treatment of Kidney Stones >2 cm: A Review of the Literature Yavuz Tarik Atik, Haci Ibrahim Cimen
+ Immunotherapy in Prostate Cancer: Recent Advances and Future Directions Ida Silvestri et al.
+ Physiotherapy in Post Neobladder Voiding Dysfunction in the Treatment of Malignant Neoplasm Carla Maria de Abreu Pereira et al.

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Congress Review

Review of the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA) 56th Annual Meeting 2019

Location: Hungexpo, Budapest, Hungary

Date: 13th – 16th June 2019

Citation: EMJ Nephrol. 2019;7[1]:12-24

The 56th ERA-EDTA congress showcased an impressive range of sessions, abstract presentations, and other activities for the delegates, who attended the congress from across the world. The EMJ congress team was among them, and we are delighted to report the latest news and updates from the congress directly to our readers. Top news stories from the congress are herein brought to you by our editorial team, who have curated the most pressing and important stories for your reading pleasure. Find out about novel biomarker DKK3 and its potential for predicting acute kidney injury; learn about the impact of employment status on mortality rates following dialysis; and take things interdisciplinary with the news of how diabetes drug linagliptin improves albuminuria in diabetic patients.

The theme of the congress this year was 'precision nephrology', with the committee eager to use this concept to focus not only on what we know already, but on what we need to know in order to deliver the very best care to patients. In his welcome address, congress co-president György Reusz described the "exceptional scientific programme" and commented on the delegates' opportunity to "see Budapest at its best," adding that "the rich history of the city combined with a vivid cultural milieu is waiting for ERA-EDTA visitors." Indeed, according to the Central Statistics Office, 12.5 million tourists visited Budapest in 2018, demonstrating its popularity as a destination. You can read our exclusive interview with Prof Reusz in our Interviews section, in which he details his role as President of the Hungarian Society of Nephrology, the role of national societies in shaping future generations of nephrologists, and his highlights from the ERA-EDTA congress.

More than 2,000 abstracts were submitted for consideration to ERA-EDTA this year, demonstrating the high level of research and the true reach of the congress to so many people around the world. Hot topics included hypertension, nephrolithiasis, chronic kidney disease - lab methods, pathophysiology,

anaemia, nutrition, and rehabilitation; paediatric nephrology; and renal transplantation to name just a few. In our Abstract Review section, our editorial team have hand-picked some of the abstracts we were most impressed by and invited the presenters to write a summary of their research and the abstract presentation at the congress. Read about the Hungarian Vasculitis Registry and the results from the first 5 years of the trial, the impact of chronic kidney disease on the hepatic clearance of citalopram, and changes in intraocular pressure during haemodialysis. The potential of these exciting presentations to one day impact clinical practice and improve patient care for people across the globe cannot be underestimated, and it is our great privilege to work with the authors to disseminate their research to our readers.

"In his welcome address, congress co-president György *Reusz described the "exceptional scientific programme"*

In addition to the abstract summaries, plenary lectures, and symposia, ERA-EDTA recognised some of the most outstanding researchers with awards at this year's congress. Dr Olivier Devuyst, University of Zürich, Zürich, Switzerland, was awarded the ERA-EDTA Award for Outstanding Basic Science Contributions to Nephrology for his work in demonstrating the role played by aquaporins in peritoneal dialysis (PD), as well as the development of preclinical strategies to streamline the process of dialysis and reduce structural damage in the peritoneal membrane. Prof Claudio Ronco, International Renal Research Institute, St Bortolo Hospital, Vicenza, Italy, was awarded the ERA-EDTA Award for Outstanding Clinical Contributions to Nephrology for his exceptional work in critical care, extracorporeal therapies, PD, and the development of novel devices such as CARPEDIEM for neonatal dialysis. In addition, Dr Rebecca Herzog, Medical University of Vienna, Vienna, Austria, was recognised with the ERA-EDTA Stanley Shaldon Award for Young Investigators after her work focussing on PD, including the development of a novel PD-fluid, discovery of the role of a specific post-translational protein modification in PD, and revealing the PD effluent proteome. Hearty congratulations to all the winners from all of us here at EMJ.

ERA-EDTA 2019 REVIEWED →

Chronic Kidney Disease and the Mission of ERA-EDTA

Globally, 850 million people are affected by kidney diseases, with chronic kidney disease (CKD) afflicting an estimated 10–11% of the European population. These startling realities were presented by Prof György Reusz, the Congress President of the 56th Congress of the ERA-EDTA and reported in a ERA-EDTA press release, in order to emphasise the need for spirited discussion between the population and policymakers, and to encourage the urgent formation of preventative measures.

The increasing prevalence of CKD cases can in part be attributed to demographic factors, such as the ageing general population, yet this does not fully explain the upward trend. CKD is subject to multifactorial regulatory input from a multitude of other conditions, including obesity, hypertension, and diabetes. This paints a complex picture in which the management of other conditions must consider additional implications for CKD progression.

The risk that CKD poses to public health is often underappreciated, often in spite of epidemiological and economic significance: dialysis, a common endpoint for patients living with CKD, incurs annual costs of approximately €60,000–80,000 per patient. This neglected attention may arise from the fact that prognostic signs for CKD remain sparse until an advanced stage has progressed, at which point preventative measures are ineffective. Couple this with the general misconceptions amongst the general population and medical community regarding CKD risk, and it easy to understand how an international health burden has grown, and indeed, continues to grow.

This recognition, however, does present ample opportunities for the dissemination of information and collaboration of efforts. "We see enormous potential in the field of early detection, especially, because it can stop the disease from advancing, or slow its progress at least," explained Prof Reusz to the international ensemble of nephrologists. Through improving CKD prevention, and heightening the profile of the disease, ERA-EDTA declared their key objective for this year's congress and set the stage for days of inspiring discussion.

"We see enormous potential in the field of early detection..."

Promise of New Treatments on the Horizon for Alport Syndrome

NEW therapies for Alport syndrome (AS) could be just around the corner, according to a study presented at ERA-EDTA 2019 and reported in a ERA-EDTA press release. In their analysis, the authors set out five reasons why the disease is an attractive area for drug development.

The first reason highlighted is that studies into AS may provide fresh insights into the causes of chronic kidney disease (CKD), and therefore contribute to efforts to find new therapies for this condition. This is because AS leads to progressive proteinuria, renal fibrosis, and kidney failure, so findings may be extrapolated to other more common causes of CKD.

The researchers also note that orphan designation will be given to any new drug approved for AS, which will encompass benefits for pharma companies such as a shortened approval timeline and a period of market exclusivity. There is also a large number of patients who would benefit from new treatments for AS, with it being the second most frequently inherited kidney disease after autosomal dominant polycystic kidney disease (ADPKD). Additionally, clinical trials for this condition should be easier to facilitate as AS patients are young and have very few comorbidities. The final factor is that there is currently no approved treatment for AS, meaning there is tremendous scope to help patients with the condition. Currently, the only recommended form of management is renin –angiotensin system blockade.

"A specific disease-modifying therapy for AS remains an unmet need, but I am sure this will change, because AS has become a very attractive target for pharmaceutical companies to target," confirmed lead author Prof Rosa Torra, Fundacio Puigvert, Barcelona, Spain.

There have indeed been numerous insights in recent years into AS, revealing crucial information that could help facilitate drug development. The researchers believe that these could pave the way for more effective clinical trial endpoints in AS in the future, rather than decline in glomerular filtration rate levels.

"Similarly to other renal diseases, this is probably too late an endpoint to make a significant impact on the course of the disease," explained Prof Torra. "Theoretically, treatment prior to the appearance of renal fibrosis offers more promising long-term renal outcomes. GBM aspect and degree of fibrosis on renal biopsy as well as proteinuria could be excellent endpoints for clinical trials."

Studies Vital to Prove Efficacy of PCSK9 Inhibitors in Chronic Kidney Disease

PATIENTS with advanced chronic kidney disease (CKD) are routinely excluded from clinical trials that aim to reduce the progression of cardiovascular (CV) disease despite this patient population being at high risk of CV mortality. As such, there is little evidence to suggest that the current gold standard treatment of lipid-lowering therapy would benefit patients on maintenance haemodialysis, and in addition reduced kidney function could make patients more susceptible to statin-related adverse events including myopathy.

In a study reported in a ERA EDTA press release dated 13th June 2019, researchers have called for mandatory studies to investigate a novel therapy that could address this persistent problem in CKD patients. Proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) is a protein that, when released, reduces the ability of the body to clear low-density lipoprotein (LDL) from circulation by blocking the expression of LDL-receptor on the surface of liver cells. Monoclonal antibodies evolocumab and alirocumab are currently approved PCSK9 inhibitors and are considered a novel therapy for lowering the levels of LDL in patients, a known contributor to CV disease in both the general population and CKD patients.

"Specific studies in CKD patients are mandatory to prove the efficacy and safety of PCSK9 inhibitors and to determine their ability to improve outcomes in these patients."

Both of these antibodies have lowered the risk of CV events in large clinical trials. Their capacity for lowering LDL was not linked to baseline kidney function, and had positive effects on patients diagnosed with moderate CKD. Although this is positive news for many patients with kidney disease, those patients with very advanced CKD and thus severely impaired kidney function were not included in these studies. Since this population is at the highest risk of CV disease, it will be important for future studies to assess the efficacy of the antibodies in these patients.

Commenting on the results, Thimoteus Speer, Department of Internal Medicine IV, Nephrology and Hypertension, Saarland University Medical Centre, Homburg/Saar, Germany, said: "In particular, in patients with advanced CKD, the high annual costs of therapy with PCSK9 inhibitors have to be balanced against weak evidence for a benefit," adding "Specific studies in CKD patients are mandatory to prove the efficacy and safety of PCSK9 inhibitors and to determine their ability to improve outcomes in these patients."

Is a New Approach to Dialysis Clinical Trials Needed?

HISTORICALLY, the success of randomised clinical trials (RCT) for new treatments for end-stage renal disease (ESRD) has not been comparable to the results of other diseases. Whether the results were negative or inconclusive, the majority of ESRD RCT have not culminated in much hope for ERSD patients. Analyses from a systematic review reported in a ERA-EDTA press release suggest that new approaches to these RCT are needed, which will improve many aspects of the RCT themselves and, hopefully, the results that come from them.

Investigating trial design and outcome measures of RCT that involved a total of 10,713 ESRD patients, the review concluded that pragmatic clinical trials (PCT) and patient-centred outcomes (especially improved quality of life) may provide the best chance of clinical improvement for the patients and the testing of new therapeutic interventions. Not only will PCT improve external and internal validity, but also be more representative of the diverse and complex ERSD population by having broader inclusion criteria, of which the traditional framework of RCT does not allow.

"The recent emergence of various RCT designs could aid in making ESRD clinical trials more successful."

Prof Csaba Kovesdy, author of the review entitled 'Clinical trials in end-stage renal disease-priorities and challenges' commented: "The recent emergence of various RCT designs could aid in making ESRD clinical trials more successful." PCT involve clinically relevant comparators, evaluation of interventions within clinical practice, and the testing of practical, meaningful outcomes. Feasibility of PCT in the haemodialysis population can be achieved by clustering patients within dialysis units and testing of medical and technical interventions within the framework of routine clinical practice.

Prof Kovesdy concluded that: "The application of such novel RCT designs could result in benefits including reduced trial cost, the examination of a broader, more representative population, and the testing of a higher number and more clinically relevant interventions, which is really needed."

Mortality Rate Following Dialysis could be Impacted by Employment Status

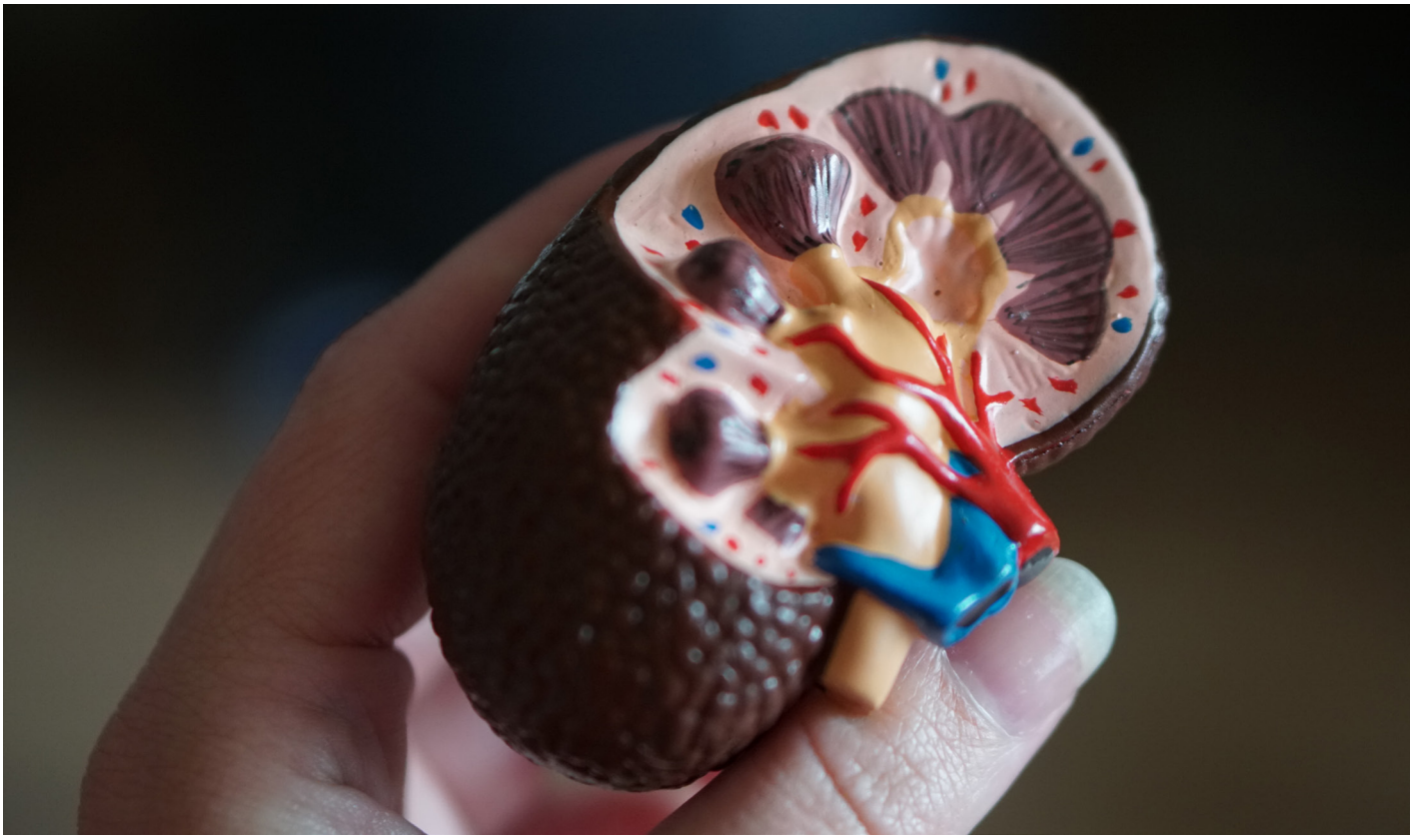
EMPLOYMENT during the 6 months preceding dialysis was associated with a higher survival rate in a retrospective study reported in a ERA-EDTA press release dated 14th June 2019. The study analysed patients who had undergone dialysis and found that those who had not been in employment for 6 months prior to the treatment had a higher rate of mortality.

The study analysed 496,989 patients in the USA who had initiated maintenance haemodialysis from 2006–2015. They looked at the employment status of these patients and found that 26% (n=129,622) had been working prior to starting dialysis, but this fell to 15% when dialysis began. While it is to be expected that the older patients were less likely to maintain a job throughout the treatment, there was also a social aspect to consider, such as female populations who became unemployed more frequently. Results showed that patients who lost their jobs presented with a significantly higher death rate than those who had been in employment for at least 6 months before the dialysis began ($p<0.0001$).

Quality of life is impacted by state of employment for most people; haemodialysis patients are no exception to this. Working can provide social support, a stable financial position, and self-esteem, which in turn all raise quality of life. Those who are unemployed can face difficulties in both the social and financial aspects of their lives and can experience psychological and physical ailments. They can experience depression and drug and alcohol abuse.

Remaining in employment throughout the 6 months prior to initiation of dialysis was associated with higher rates of transplantation and better protection against mortality, but it is important to remember that these data can be interpreted in several ways: were these patients unemployed because they had been extremely ill before dialysis and therefore less likely to survive, regardless of job status? The authors recognised the limitations due to the retrospective nature; therefore, they could only draw conclusions based on associations between the variables that were known.

"...patients who lost their jobs presented with a significantly higher death rate than those who had been in employment for at least 6 months before the dialysis began."



Targeting Metabolic Acidosis Slows Renal Decline in Late-Stage Chronic Kidney Disease

METABOLIC acidosis, a condition in which the kidneys are unable to maintain normal acidic balance in the body, is common in patients with late-stage chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR]: <30 mL/min/1.73 m^2). As well as kidney function decline, it is associated with several dangerous comorbidities, including insulin resistance, muscle wasting, and bone disease. Results of the UBI trial, reported in a ERA-EDTA press release, attest to the benefits of correcting this condition with sodium bicarbonate to improve the overall clinical picture in these patients.

A cohort consisting of 740 patients with Stage 3b or 4 CKD were given either sodium bicarbonate (376 patients) or standard of care (364 patients). Following 3 years, the sodium bicarbonate arm of the study experienced significantly less doubling of creatine (6.6% compared to 17.0%), translating into a 64% relative risk reduction in kidney disease progression (hazard ratio [HR]: 0.36; 95% confidence interval [CI]: 0.22–0.58; p<0.001).

The likelihood of starting renal replacement therapy (RRT) was also diminished in the sodium bicarbonate-treated group (6.9% versus 12.3%), a risk reduction amounting to 50% (p=0.004; HR: 0.5; 95% CI: 0.31–0.81; p=0.005). A 57% relative risk reduction was also seen in the sodium bicarbonate-treated group, and importantly, the treatment was well-tolerated and exhibited no significantly adverse effects on total body weight or hospitalisations.

Lead investigator Dr Antonio Bellasi, Department of Nephrology and Dialysis, S. Anna Hospital, Como, Italy, concluded that "[Our] study shows that that this very cost-effective treatment is safe and improves kidney and patient survival." This study serves as a brilliant example of finding novel uses for drugs that have pre-established safety profiles and are widely administered.

Increased Cholecalciferol Dosage Reduces Risk of Fracture Following Kidney Transplant

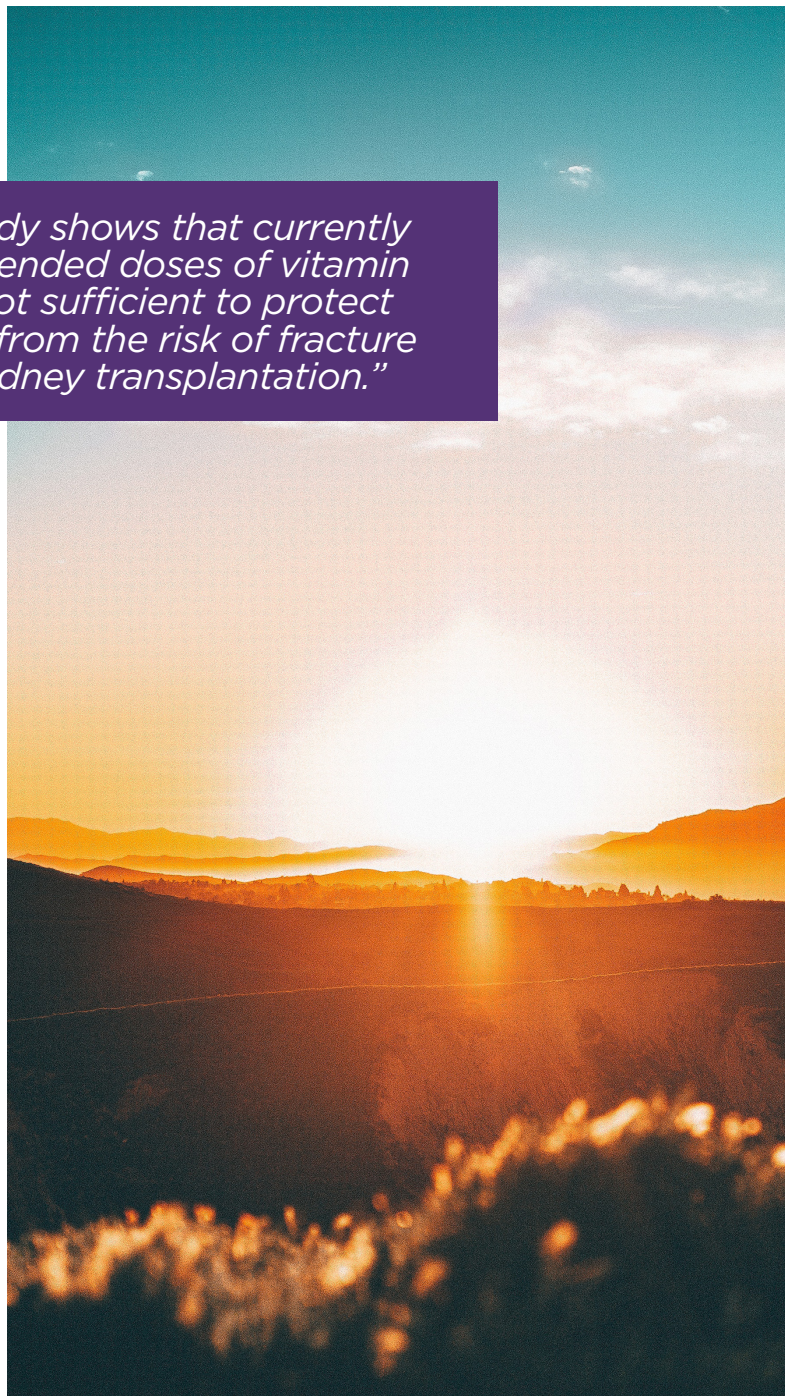
KIDNEY transplant remains the gold standard of treatment for patients with kidney failure, increasing survival rates and quality of life. However, this treatment option is not without its drawbacks, one of which being an increased risk of fractures. Now, building on previous research, the VITALE study has shown that an increase in supplementary vitamin D, greater than previous recommendations, may safely lower the risk of fractures. The results from this study were revealed in a ERA-EDTA press release on 14th June, 2019.

Chronic kidney disease–mineral bone disease occurs as a result of the failing kidneys being unable to maintain normal levels of parathyroid hormone, vitamin D, and blood levels of calcium and phosphate, all of which play vital roles in maintaining bone health. To counteract this, Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend correcting the vitamin D deficiency via a supplementation of vitamin D3 (cholecalciferol); dosage is based on the requirements of the general population, but there is no high-level evidence to support this measurement. Thus, the prospective, multicentre, double-blind, controlled trial, VITALE aimed to assess skeletal and non-skeletal effects of high versus low doses of cholecalciferol after kidney transplantation.

The trial enrolled 536 kidney transplant recipients (mean age: 50.8 years, 335 males), randomising them to either 100,000 IU (high dose) or 12,000 IU (low dose) cholecalciferol every 2 weeks for 2 months, before switching to monthly dosage for 22 months. 'Low dose' corresponded to a minimum recommended intake of 400 UI/day. The high dose group had significantly higher vitamin D levels than the low dose group at 24 months (43.1 [12.8] ng/mL versus 25.1 [7.4] ng/mL compared with 20.2 [8.1] versus 19.2 [7.0] ng/mL at study inclusion; p<0.0001). Similarly, the incidence of fracture was also significantly lower in the high dose group (1% versus 4% in the low dose group; p=0.02). The high dose treatment was well-tolerated, with no increased risk of vascular calcification, hypercalcaemia, or hyperphoshataemia.

Commenting on the results of the trial, lead investigator Dr Marie Courbebaisse of Assistance publique – Hôpitaux de Paris, Paris, France, commented: "Our study shows that currently recommended doses of vitamin D are not sufficient to protect patients from the risk of fracture after kidney transplantation."

"Our study shows that currently recommended doses of vitamin D are not sufficient to protect patients from the risk of fracture after kidney transplantation."



Novel Biomarker Could Predict Acute Kidney Injury

DESPITE acute kidney injury (AKI) being a common complication of cardiac surgery with an incidence of 7–40%, it is poorly predicted and has a big impact on intensive care unit stays and mortality. Severity of AKI can fluctuate from subclinical to severe, requiring renal replacement therapy with dialysis. To prevent the late diagnosis and development of severe AKI, sensitive biomarkers need to be identified. The results from an observational cohort study testing DKK3, a novel renal biomarker, were reported in a ERA-EDTA press release.

Two patient cohorts formed the study group (N=949): the derivation cohort (n=733) were patients who had undergone elective cardiac surgery at the Saarland University Medical Centre, Homburg, Germany, and the validation cohort (n=216) contained patients who were about to receive elective cardiac surgery and enrolled in the prospective RenalRIP multicentre trial.

By using urinary concentrations of DKK3: creatinine, significant improvements in AKI prediction was observed in the derivation cohort ($p<0.0001$). In the RenalRIP trial, preoperative urinary DKK3:creatinine concentrations were used to predict outcomes of AKI post-surgery. Patients with urinary concentrations of DKK3:creatinine >471 pg/mg were at a higher risk of developing AKI ($p=0.026$), persistent renal dysfunction ($p=0.0072$), and dialysis dependency ($p=0.020$).

"Urinary DKK3 can significantly improve the prediction of AKI beyond the established clinical models and available biomarkers. Measurement of urinary DKK3 might therefore represent a personalised medicine approach in patients having cardiac surgery. It gives us the chance to detect patients at risk for AKI and subsequent kidney function loss and to take care of them intensively," explained study investigator Prof Danilo Fliser, Homburg/Saar, Germany. "A DKK3-ELISA test provides relatively simple identification of at-risk patients. We think it is time to implement it in clinical practice."

"A DKK3-ELISA test provides relatively simple identification of at-risk patients. We think it is time to implement it in clinical practice."

Call Made to Increase Nephrological Research Activities

STRENGTHENING nephrological research activity was a key message from this year's ERA-EDTA Congress, and this was demonstrated by the formation of the Nephrology and Public Policy Committee (NPPC), which presented a 5-year plan to stimulate research collaboration in Europe during the event.

The NPPC was established following concerns that there are insufficient levels of nephrology research occurring. For instance, a 2013 study showed that just 2.6% of trials overall were classified as nephrology. Additionally, very few of these were diagnostic, screening, or health services research studies, with the vast majority relating to treatment (75.4%) or prevention (15.7%), reported an ERA-EDTA press release.

"Epidemiological and clinical research and public policy in Europe are generally considered to be comprehensive and successful, but there is potential for improvement and scope for new opportunities," said Prof Ziad A. Massy, Chair, NPPC. "Especially in nephrology we have to further intensify our research activities. With 850 million people suffering from kidney diseases of any kind worldwide, nephrology has to be one of the main areas of medical research."

To make the growth in research activities a reality, the NPPC, supported by the ERA-EDTA, have created a 5-year research plan. Eight action points underpin the initiative, with the aim of boosting research collaboration and grant applications under the umbrella of the ERA-EDTA.

The action points include a focus on collaborative research with the purpose of improving classification and prognosis of kidney diseases; promote active collaboration between paediatric and adult nephrologists to plan a successful transition process from paediatric to adult care of CKD; supporting the development of world-leading big data research via various methods; and the creation of a European network of kidney units to increase insights into AKI progression and complications.

One of the major aims of the plan is to use new insights gathered to highlight the urgency of tackling kidney disease throughout and to ultimately encourage a more concerted effort in this area. Prof Massy added: "Although many trials in nephrology have been initiated within the last 5–8 years, we still have to catch up. In my view it is especially important to generate epidemiologic and healthcare data in order to sensitise the public as well as policy makers to kidney diseases. It is high time to put the global spread of kidney diseases into focus."

Diabetes Medication Could Improve Albuminuria

LINGALIPTIN, the diabetes medication, was found to improve albuminuria in diabetic patients, but did not impact glomerular filtration rate (GFR) and cardiovascular (CV) risk. This was found in a late-breaking clinical trial, CAMELINA, that was presented at ERA-EDTA on the 14th June 2019. The study follows a recent development that found another class of diabetes drug, SGLT2 inhibitors, had the ability to slow the development of chronic kidney disease (CKD).

"The study clearly showed that there is a group of patients with diabetes who clearly are in need of outcome-enhancing therapies, because their prognosis is rather poor."

The multicentre, double-blind, randomised CARMELINA trial set out to assess 5 mg of the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin (LINA) in its ability to minimise CKD and CV problems in patients with diabetes, compared with placebo. DPP-4 inhibitors are often prescribed as second or third-line options for Type 2 diabetes mellitus patients who are not displaying a sufficient response to the more commonly used medication such as metformin. They work by blocking the DPP-4 enzyme responsible for destroying incretins, which stimulate insulin production; therefore, the drugs facilitate a drop in blood sugar levels.

Results showed that 646 of the 6,979 patients had renal disease due to nephrotic-range proteinuria; these patients had a 3-fold greater drop in GFR. This group were high-risk for CV events and showed poor kidney outcomes. The groups did not display a difference in loss of GFR (-6.51 per year versus placebo -7.07 per year). The drug did not impact the risk for major adverse CV events (HR:1.02; 95% confidence interval [CI]: 0.89, 1.17). A greater proportion of patients in the LINA group reverted to normoalbuminuria or demonstrated a lower urine albumin:creatinine ratio of ≥50%.

Lead investiagor Prof Wanner, Divison of Nephrology, University Hospital Würzburg, Würzburg, Germany, concluded the study: "The study clearly showed that there is a group of patients with diabetes who clearly are in need of outcome-enhancing therapies, because their prognosis is rather poor. Nephrotic-range proteinuria might be a good marker to stratify these patients. I would advise to treat these patients with SGLT2 inhibitors instead, or a combination of SGLT2 inhibitor and DPP-4 inhibitor."

Interview

Prof György Reusz

President of the Hungarian Society of Nephrology and Congress Co-President of ERA-EDTA

Q1 Please tell us a little about yourself and your role as President of the Hungarian Society of Nephrology.

The Hungarian Society of Nephrology (HSN) was founded, alongside other national societies, at a time of expansive development in nephrology, when dialysis and transplantation were moving into everyday practice, and new procedures, such as percutaneous renal biopsy and renal replacement treatments, were being introduced.

We were behind the Iron Curtain, but our pioneers worked hard, and in 1986 a European Dialysis and Transplant Association (EDTA) Congress was held in Budapest; thus, the present European Renal Association (ERA)-EDTA Congress in Budapest is a great return. I am the current HSN President (from 2012 until 2020) and we are taking part in the development of the new nephrology curriculum in Hungary and have developed guidelines for the treatment of renal diseases. The ERA-EDTA initiative to translate and adopt the European Renal Best Practice (ERBP) guidelines has been warmly welcomed by the HSN, and this was one of many opportunities for HSN and myself to engage in a fruitful collaboration with ERA-EDTA. We are supporting the Young Nephrologists Platform (YNP) programme of ERA-EDTA, working with the first president of YNP, Miklos Molnar, a young Hungarian scientist. We have also been actively involved in the national president's programmes, and, of course, our bid for the Budapest congress was positively evaluated by the ERA-EDTA council.

> "This event brings effervescence into the local scientific life and we have seen the number of scientific papers submitted from Hungary double this year."

Q2 What does co-hosting the ERA-EDTA congress mean for the Hungarian Society of Nephrology?

We hope for more visibility both in Hungary and worldwide. This event brings effervescence into the local scientific life and we have seen the number of scientific papers submitted from Hungary double this year. We are heavily involved in a campaign that connects World Kidney Day (14th March) events and the period around the congress to spread knowledge about kidney diseases and their prevention among the

population. Further, many young colleagues will have the opportunity to visit a big international congress at home. For many, this will be their first congress and we hope this will be a great experience for them.

Q3 In an increasingly globalised world, how important are national societies in shaping the development of the next generation of nephrologists? Do you see their importance changing over the coming years?

The role of the national societies differs depending on the region. Here in central Europe one of the most important tasks is to keep young doctors in the country. We are facing an unparalleled brain-drain. We are involved in adapting international standards in teaching and patient care, but we also need to strengthen their professional commitment to keep them on track. We are also actively taking part in the educational initiatives of ERA-EDTA.

Q4 Budapest is a beautiful city, rich in history and culture. What makes it such a great venue for an international medical congress?

International congresses are indeed important scientific events. However, the social part of the congress, such as the face-to-face discussions and the opportunity to network, is equally important. There are personal contacts that cannot be replaced by teleconferences or email correspondence. Budapest is an optimal site for such informal, interpersonal communications in the fine June weather, outdoors or in cosy restaurants. If you are a real fan of culture you can find many exhibitions from antique culture, to medieval arts and contemporary exhibitions. A walk in the heart of Budapest will show you the richness built from centuries of architecture.

Q5 As Co-President of this year's congress, can you tell us how the scientific programme is developed? What's new at the ERA-EDTA congress this year?

The scientific programme is indeed the heart and the engine of the congress. For me, it was a great experience to work with Alberto Ortiz, this year's President of the Scientific Committee; Carmine Zocalli, ERA-EDTA's President; and Danilo Flieser, the head of the paper selecting committee. We tried to pay attention to every detail. The final programme reflects the results of our great work, and we have to also mention the role of the ERA-EDTA staff for taking the immense administrative burden from our shoulders.

"...our changing view about mono and polygenic inheritance with modifying siRNA and the interplay of multiallelic determinates is a very hot topic and an intellectual challenge."

Q6 What data are you most looking forward to seeing presented at the ERA-EDTA congress?

The programme has been conceived to present updates in as many fields as possible, despite the limited time frame of 4 days. Everyone has their priorities: the genetics of kidney diseases, cardiovascular consequences of chronic kidney disease, biological treatments, and glomerular diseases are a few examples.

The evolution of molecular genetics and our changing view about mono and polygenic inheritance with modifying siRNA and the interplay of multiallelic determinates is a very hot topic and an intellectual challenge.

Further, given the new epidemiologic burden of obesity, hypertension, and diabetes, and its impact on the general population, studies exploring new strategies to overcome the consequences of diabetes are also of crucial importance. I'm expecting to see interesting animal experiments, lab results, and clinical data on this subject.

Q7 How has the ERA-EDTA Congress changed since you first began attending? How would you like to see it improve in the future?

The EDTA Congress has developed from a 'European Dining and Touristic Association' (as it was jokingly called in the past) to a valuable scientific conference presenting the latest scientific developments. It has become an

immense showcase of the best research labs and clinical research groups. It is always difficult to surpass the achievements of previous congresses, but the evolution of science helps us as every year brings new discoveries, and new diagnostic and treatment strategies. New evidence is described and proven. From that point of view we have only to carefully listen to the voice of the future...

Q8 The congress will include a session on the gut–kidney–cardiovascular axis. What role does interdisciplinary collaboration play in modern nephrology practice, especially for studying topics such as this?

The human and their microbiome is a very complex symbiosis. We are beginning to understand some aspects of the interplay between the gut microbiome and the human body. There are reciprocal effects; for example, the impact of the uraemic environment on the gut and the effect of altered bowel bacteria on the body. However, we have to keep in mind that other organs, previously regarded as sterile (such as the urinary bladder), have their own microbiome, with new paradigms emerging concerning urinary tract infections. Thus, an interdisciplinary approach will certainly enrich our knowledge and later, perhaps, our everyday practice.

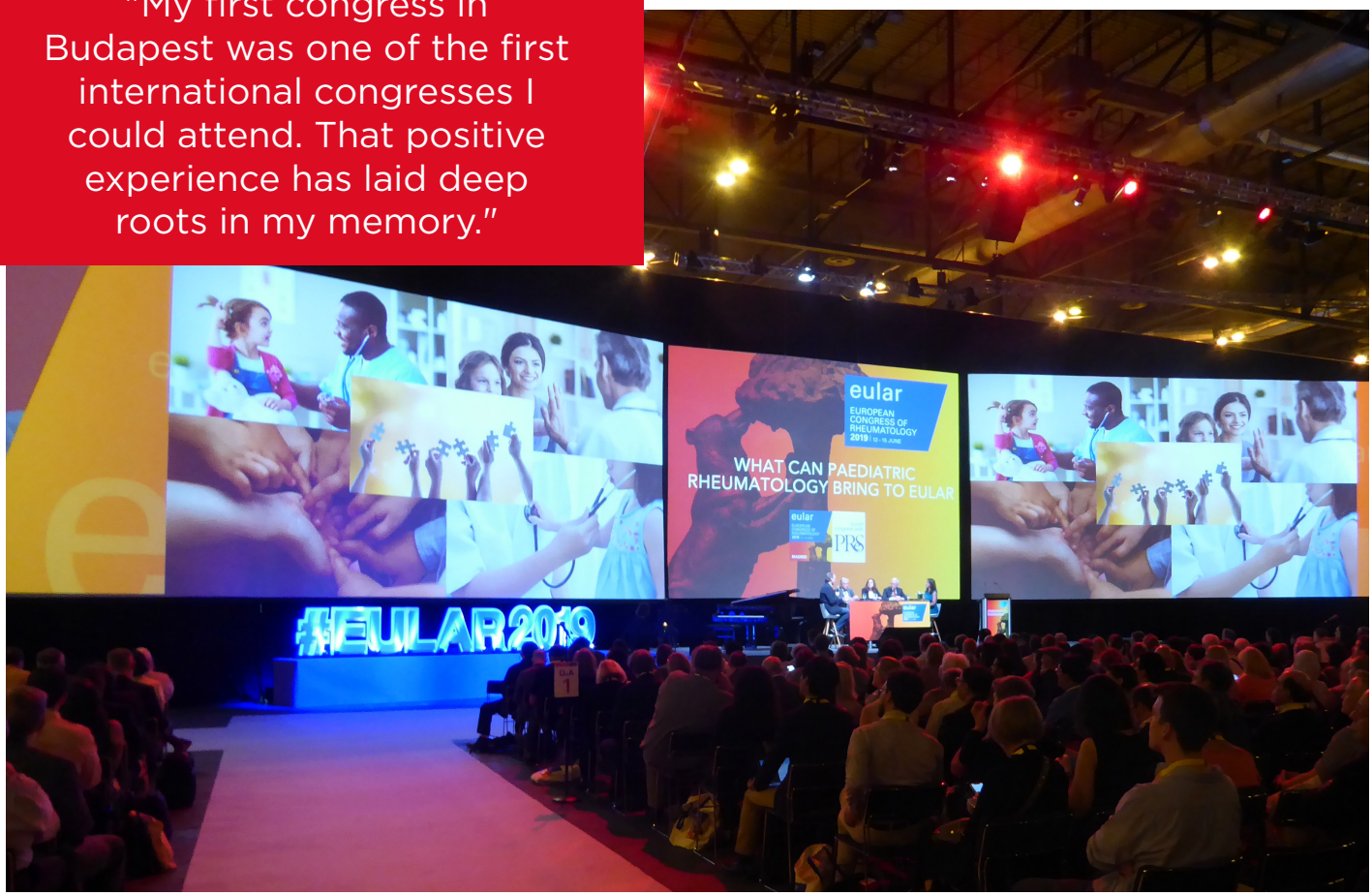
Q9 What topics would you like to see receive more coverage in the world of nephrology, or in medicine more generally?

The number of topics covered at the congress are already embarrassingly high, but I think this is necessary and allows one to find their topic of interest. One also has their preferences in terms of topics. Prevention and management of acute kidney injury and of progression of kidney disease, the relation of heredity, and the environmental effects are some topics that deserve the attention of the broader medical community.

Q10 What is your favourite memory of ERA-EDTA?

My first congress in Budapest was one of the first international congresses I could attend. That positive experience has laid deep roots in my memory. I hope that today's youngsters will feel like this when they later remember our current congress.

"My first congress in Budapest was one of the first international congresses I could attend. That positive experience has laid deep roots in my memory."



Survival After End-Stage Renal Failure: Preventing Cardiac Death in End-Stage Renal Disease Patients

This symposium took place on 14th June 2019, as part of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Congress in Budapest, Hungary

Chairperson: Dr Natalie Borman[1]

Speakers: Dr Allan Collins,[2] Dr Maria Fernanda Slon,[3] Dr Nicholas Sangala[1]

1. Wessex Kidney Centre, Portsmouth, UK
2. NxStage Medical Inc., USA
3. Hospital de Navarra, Pamplona, Spain

Disclosure: Dr Collins is an employee of Fresenius Medical Care. Other authors are members of the NxStage European Medical Board and have received speaker honoraria. The reader should check the package insert of all drugs and devices for indications, dosage, warnings, and precautions.

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Meeting Summary

At the 56th European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Congress, held in June 2019 in Budapest, Hungary, physicians from the USA, UK, and Spain presented an educational symposium entitled 'Survival After End-Stage Renal Failure: Preventing Cardiac Death in End-Stage Renal Disease Patients.' During this symposium, physicians discussed concepts underlying dialysis as a chronic cardiovascular disease state; cardiovascular disease challenges with volume overload, hypertension, and heart failure; the challenge of fluid management in intermittent haemodialysis; and the effect of more frequent therapy on volume and symptom control. This review summarises the symposium.

Dialysis as a Chronic Cardiovascular Disease State

Doctor Natalie Borman

Haemodialysis was developed to alleviate symptoms due to accumulating uraemic toxins and acute fluid overload in patients with advancing chronic kidney disease and end-stage renal disease (ESRD); however, this life-saving treatment has ironically created a unique chronic disease state in dialysis-dependent patients. During the last 40 years, the leading cause of death in dialysis patients has shifted from renal failure to cardiovascular disease.[1,2] This chronic

disease state requires a shift in philosophy regarding the dialysis prescription. In particular, the dialysis prescription should be aimed not only at achieving adequate small solute clearance, but also by slowing the progression of cardiovascular disease and improving the patient's tolerance of therapy.

Fluid overload significantly contributes to the development of cardiovascular disease during dialysis through several physiological pathways.[1,3] First, chronic fluid overload contributes to uncontrolled hypertension, left ventricular hypertrophy, and cardiac failure.[4] Second, relatively rapid ultrafiltration to remove extracellular fluid is associated with myocardial stunning, intradialytic hypotension, and increased risk of death.[5] The popular thrice-weekly haemodialysis schedule includes a 2-day gap, which has been associated with increased risk of death, hospitalisation, and adverse cardiovascular events.[6-8] According to new data from the USA, approximately 79% of dialysis patients have a diagnosis of diabetes, heart failure, or cardiac arrhythmia.[9] An ESRD patient with any one of these conditions has an estimated 1.7–2.0 times greater risk of cardiovascular death than an ESRD patient without any of these conditions. An ESRD patient with two of these conditions has an estimated 2.5–3.6 times greater risk of cardiovascular death, and an ESRD patient with all three conditions has an estimated 5.0 times greater risk of cardiovascular death (Figure 1).[9]

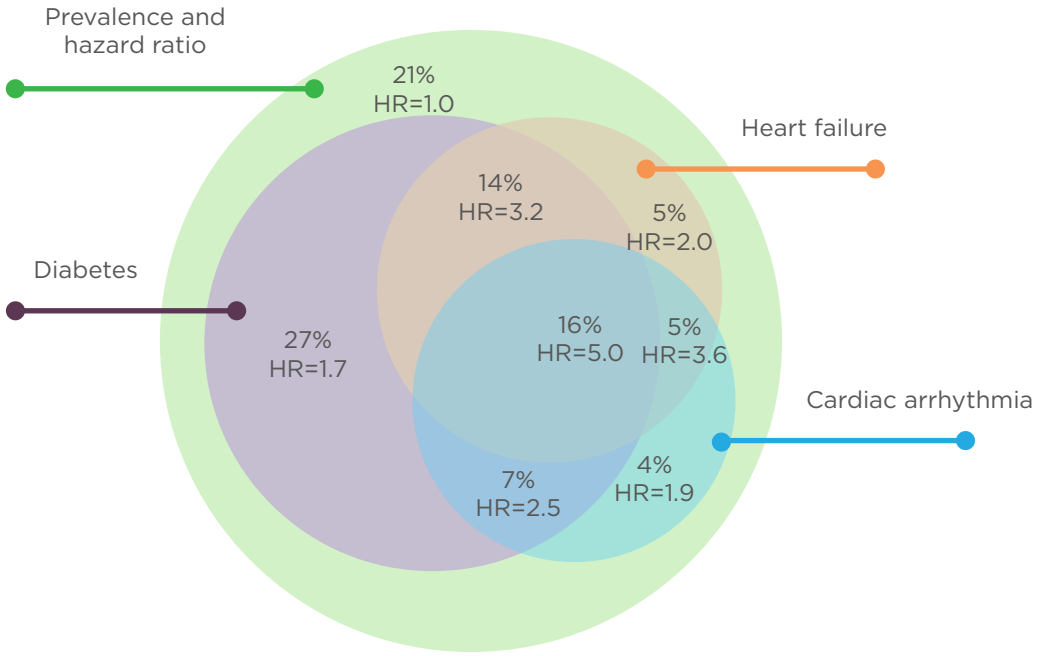

Figure 1: Stratification of cardiovascular death risk by arrhythmia, heart failure, and diabetes in a prevalent cohort of dialysis patients in the USA.[9]

HR: hazard ratio.

Cardiovascular Disease Challenges with Volume Overload, Hypertension, and Heart Failure

Doctor Allan Collins

Patients undergoing intermittent haemodialysis experience huge fluid shifts and often intradialytic hypotension, visible through right ventricular pressure tracing (Figure 2).[10] Patients undergoing conventional haemodialysis are typically in a state of interdialytic pulmonary hypertension (right ventricular systolic blood pressure >30 mmHg). Systolic blood pressure dramatically decreases to near-normal range during dialysis treatment, but quickly returns to an elevated state during the interdialytic interval. The long interdialytic interval inherent in thrice-weekly dialysis results in patients experiencing persistent volume expansion and severe pulmonary hypertension (right ventricular

systolic blood pressure >40 mmHg). This cycle of volume loading and unloading creates markedly abnormal cardiac pressure. Moreover, loading between treatments creates wall stress tension, leading to myocardial injury, cytokine production in the heart, left ventricular hypertrophy, and systolic and diastolic dysfunction.

During haemodialysis, a number of patient-related and treatment-related factors contribute to an ultrafiltration rate (UFR) that exceeds the plasma refill rate, leading to the decrease of effective arterial blood volume, the reduction of cardiac filling, the decline of cardiac output, and ultimately intradialytic hypotension. A number of interventions are recommended to alleviate intradialytic hypotension, including reduction of UFR and adjustment (or withdrawal) of antihypertensive medications.[11] However, the latter of these recommendations often leads to discontinuation of cardioprotective medications, such as beta blockers and renin-angiotensin system inhibitors, which have been associated with lower risks of morbidity and mortality in patients with advanced kidney disease.[12] Thus, although this action alleviates intradialytic hypotension, it removes treatments which address heart rhythm, cardiac stress, and chronic hypertension. Alternative haemodialysis regimens are needed to treat heart failure and diastolic dysfunction in the dialysis population.

Challenge of Fluid Management in Haemodialysis

Doctor Maria Fernanda Slon

Clinical practice guidelines recommend a UFR during haemodialysis that achieves volume control and minimises haemodynamic instability and intradialytic symptoms, yet the major factors influencing volume control (i.e., accurately measuring dry weight, limiting interdialytic weight gain, and minimising the fluid removal rate) are challenging to manage and are often unaddressed in dialysis patients.[13] There is growing evidence that high UFR is associated with intradialytic hypotension, myocardial stunning, hypervolaemia, cardiac structural changes, and greater risk of morbidity and mortality.[8,14-17] However, the optimal range of fluid removal rate is not clear.

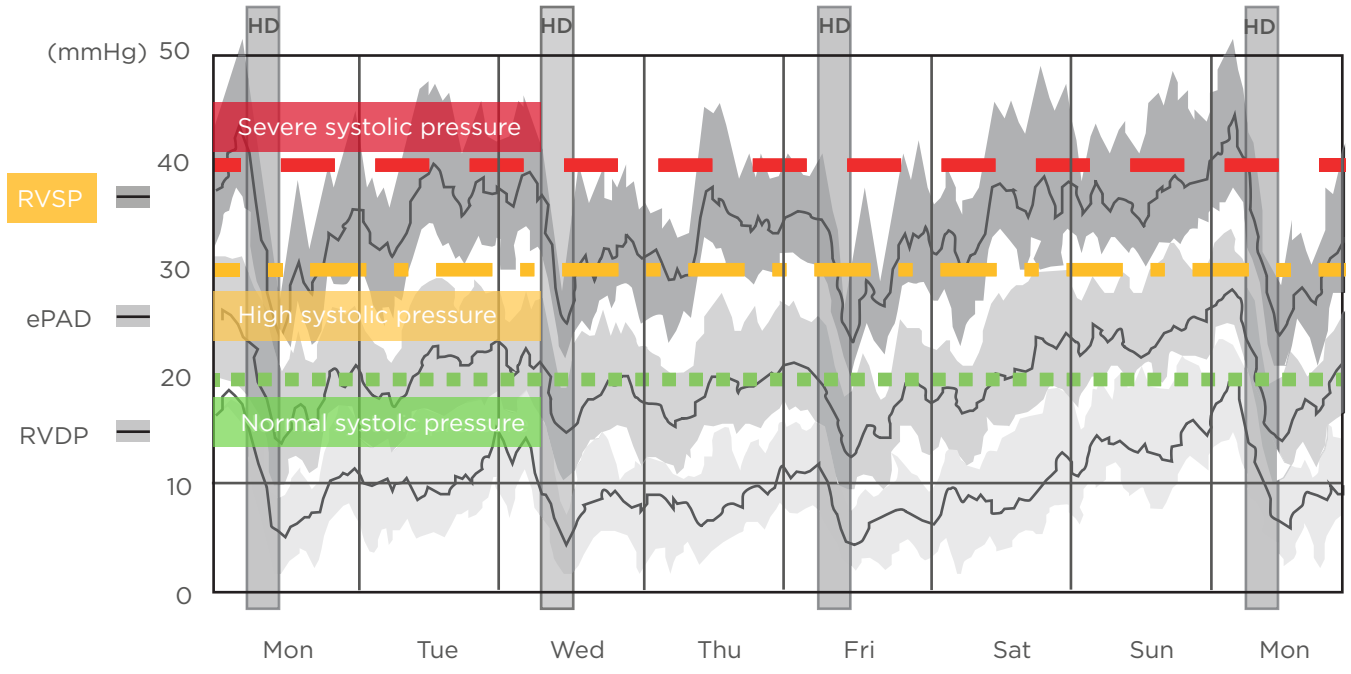

Figure 2: Changes in right ventricular pressures between haemodialysis sessions recorded by an implantable haemodynamic monitor[10]

ePAD: estimated pulmonary artery diastolic pressure; HD: haemodialysis; RVDP: right ventricular diastolic pressure; RVSP: right ventricular systolic pressure.

A number of studies have attempted to evaluate the UFR threshold above which patient survival is impaired. In a study of prevalent haemodialysis patients, Flythe et al.[14] demonstrated that the risk of all-cause and cardiovascular mortality began to increase at UFR >10 mL/hour/kg regardless of the status of congestive heart failure. However, Chazot et al.[8] demonstrated that even a moderate UFR was associated with increased risk of death among prevalent haemodialysis patients; patients with UFR >6.8 mL/hour/kg experienced a significantly greater risk of all-cause mortality than patients with UFR <6.8 mL/hour/kg.[8] In a study of incident patients, Kim et al.[15] reported linear associations between UFR and both all-cause and cardiovascular mortality. Finally, a large retrospective cohort study by Assimon et al.[16] confirmed a robust association between higher UFR and higher risk of death.

UFR is also related to recovery time through its direct effect on symptomatic hypotension and myocardial stunning. Moreover, a wide variety of symptoms during haemodialysis are frequently related to high UFR, including fatigue, intradialytic hypotension, cramps, and post-dialysis dizziness.[18,19] These symptoms are significant not only as determinants of health-related quality of life, but also through an association between longer post-dialysis recovery time and greater risk of all-cause mortality.[20]

The challenge of mitigating UFR can be achieved either by reducing interdialytic weight gain through increased dialysis frequency or by extending dialysis treatment time.[17] In patients with large weight gains or high UFR, clinical practice guidelines in the USA recommend more frequent or longer haemodialysis sessions in order to achieve optimal volume control and tolerance of dialysis sessions.[13] The Frequent Hemodialysis Network (FHN) Daily and Nocturnal Trials demonstrated that the per-treatment incidence of intradialytic hypotension was lower with intensive haemodialysis compared to conventional haemodialysis, and that intradialytic hypotension was significantly less likely during longer haemodialysis sessions.[21] Likewise, the FREEDOM study found that home haemodialysis for five or six sessions per week led to a clinically significant reduction in recovery time during 1-year follow-up.[22] In general, lowering UFR through more frequent or longer dialysis sessions seems to lead to an improvement in recovery time, quality of life, and all-cause survival. Thus, there is evidence to support the contention that increasing treatment frequency, as well as cumulative treatment time, is an effective way to address volume control and tolerance of dialysis sessions and lower risk of dialysis-related morbidity and mortality.

More Frequent Therapy: The Key to Volume and Symptom Control?

Doctor Nicholas Sangala

More frequent dialysis sessions may control volume overload, cardiovascular risk, and patient-related symptoms among a diverse patient population with varying states of physiology, comorbidity, and lifestyle.[1,3,4] This is increasingly important as patients with more complex comorbidity are reaching ESRD and requiring haemodialysis. In fact, the most frail and highly comorbid patients may experience the greatest improvement in symptoms with longer and more frequent therapy, as the therapy can alleviate dialysis symptoms such as cramps, lethargy, headaches, light-headedness, and prolonged recovery, and reduce medical complications such as intradialytic hypotension, interdialytic hypertension, and cardiac instability.

Patients receiving dialysis at home more than three times per week through Wessex Kidney Centre in Portsmouth, UK, regularly record patient-related symptoms on a digital platform. Over a period of 12 months, pre and post-dialysis systolic blood pressure, UFR, symptoms, and recovery time were recorded across 9,666 consecutive dialysis sessions in 79 patients. Despite an average age of 56 years (range: 21–77 years) and an average Charlson Comorbidity Index of 4.2 (range: 2.0–9.0), patients experienced intradialytic hypotension in only 2.8% of dialysis sessions, cramps in 3.4%, and headaches in 5.2%. Greater symptom severity appeared to be associated with greater haemodynamic instability, as measured by the percent reduction in systolic blood pressure during dialysis. Recovery time also appeared to have a strong relationship with haemodynamic instability; patients who recovered immediately after dialysis had the least haemodynamic instability, whereas

patients who required >6 hours to recover after dialysis had the most haemodynamic instability (Figure 3). Finally, patients who reported feeling below average immediately after dialysis experienced significantly more haemodynamic instability than patients who reported feeling average or above average. Although there did not appear to be a relationship between symptom severity and UFR, dialysis sessions were almost always performed with a very low UFR (i.e., <6 mL/hour/kg).

The significance of haemodynamic instability on symptom control in these data support an emphasis on hydration status and the amount of fluid in the extracellular space at the start of dialysis. For example, examination of patient-level data from the Wessex Kidney Centre cohort suggests that individuals experience more severe symptoms and more haemodynamic instability with lower post-dialysis weights. Identifying an optimal target weight can help achieve asymptomatic dialysis with minimal haemodynamic instability.

UFR and hydration status are key indicators of fluid management, which can be managed effectively by altering treatment frequency. Increasing haemodialysis frequency can help improve stability, improve blood pressure control, reduce symptoms, meet individual ultrafiltration goals, allow for the use of cardioprotective medications, eliminate fluid overload resulting from a 2-day gap in treatment, and break the volume overload cycle. In doing so, patients may experience lower risk of cardiac death during long-term dialysis.

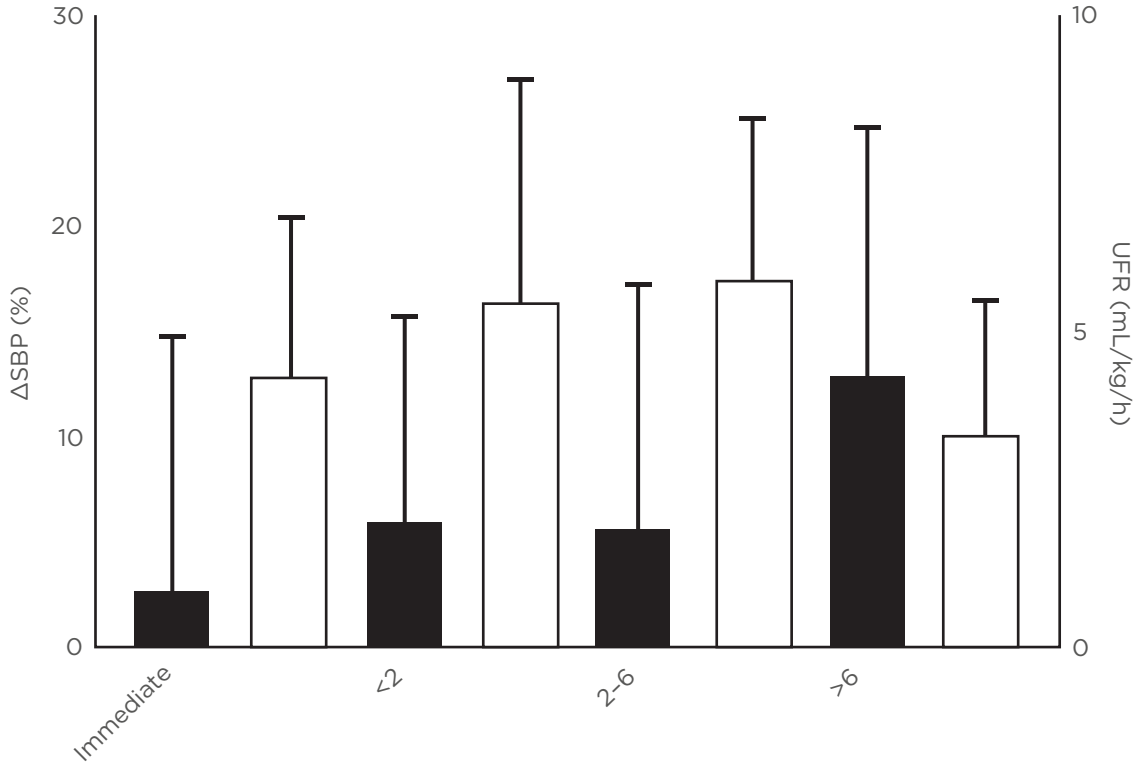

Figure 3: Individuals taking longer to recover after dialysis have poorer haemodynamic stability during dialysis (unpublished data).

SBP: systolic blood pressure; UFR: ultrafiltration rate.

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Abstract Reviews

From polyangiitis to allo-haemodialysis, read some of our top picks from the ERA-EDTA abstract presentations here.

Renal Involvement in Eosinophilic Granulomatosis with Polyangiitis

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Keywords: Eosinophilic, granulomatosis, polyangiitis.

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BACKGROUND AND AIMS

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic necrotising vasculitis affecting small to medium sized vessels, characteristically associated with asthma and eosinophilia.[1-3] Renal involvement occurs in approximately 25% of EGPA cases.[4,5] Presentation includes focal and segmental necrotising crescentric glomerulonephritis (NCGN),[4,6] eosinophilic interstitial infiltrates,[4,7] or obstructive uropathy[4] caused by vasculitic involvement of the ureters. The aim of this study was to analyse the prevalence, clinical manifestations, and outcomes of EGPA patients with renal involvement.[8]

METHODS AND RESULTS

The authors retrospectively analysed 142 patients with EGPA classified using American College of Rheumatology (ACR) and consistent with Chapel Hill Consensus 2012 definitions. Patients were selected with renal involvement defined by the presence of A) renal insufficiency serumcreatinine(SCr)>97uMol/L,orB)haematuria and/or proteinuria (>1+ in urinalysis), or C) obstructive uropathy.

Eleven (7.74%) patients with renal involvement (Table 1), 8 men and 3 women, with a mean age of 58.3±8.8 years, were identified. Median time of follow-up was 10.8±9.5 years. Seven were anti-neutrophil cytoplasmic antibody (ANCA) positive, six with myeloperoxidase (MPO), and one proteinase 3 (PR3)–ANCA. Three presented with rapidly progressive kidney injury with SCr

>290 uMol/L, six with SCr >117 uMol/L, and two had normal SCr (44–97 uMol/L). Data for dipstick analysis on ten patients revealed seven with haemoproteinuria, one with proteinuria, and two with normal urinalysis. Renal biopsy was performed in six patients, showing three with NCGN, two had both NCGN and tubulointerstitial nephritis (TIN) with eosinophil infiltrates, and one had TIN with eosinophil infiltrates alone. All the patients with NCGN were ANCA positive, while the patient with TIN alone was ANCA negative. Two patients had obstructive uropathy due to ureteric stenoses. Patients received immunosuppressant therapy with prednisolone, cyclophosphamide, rituximab, mycophenolate mofetil, azathioprine, methotrexate, and plasma-exchange (Table 1). At the end of follow-up, two patients were renal transplant recipients, five had chronic kidney disease, and four maintained normal kidney function.

Table 1: Renal Involvement in eosinophilic granulomatosis with polyangiitis.

Patient Number	Sex	Age (years)	kSCr (uMol/L)	ACR (mg/uMol)	Prot	Haem	ANCA	Renal biopsy/ imaging	Treatment	SCr and outcome	Follow-up (years)
1	Male	60	164	37.4	+	-	-	TIN	Pd+Cy	131	8.8
2	Female	63	130	20.2	+	+	MPO	NCGN Focal + TIN	Pd+Cy+RTX+AZA	Renal transplant	10.5
3	Male	70	85	12.9	+	+	MPO	NCGN Focal	Pd+Cy+RTX+AZA	86	7.6
4	Female	65	450	N/A	+	+	MPO	NCGN	Pd+AZA	189	6.3
5	Male	56	293	69.3	+	+	MPO	NCGN Crescentic + TIN	Pd+Cy+RTX+PLEX	184	0.5
6	Male	56	300	62.8	N/A	N/A	PR3	No biopsy	Pd+RTX+MMF	Renal transplant	6.2
7	Female	53	149	1.0	-	-	-	No biopsy	Pd+Cy	148	33.7
8	Male	65	138	40.5	+	+	MPO	No biopsy	Pd+Cy+MMF	80	7.2
9	Male	50	81	1.2	+	+	-	No biopsy	Pd+MMF	75	1.4
10	Male	39	138	0.5	+	+	MPO	Ureteric stenosis	Pd+RTX+AZA	93	17.1
11	Male	65	117	N/A	-	-	-	Ureteric stenosis	Pd+MTX	100	19.6

ACR: albumin creatinine ratio; ANCA: anti-neutrophil cytoplasmic antibody; AZA: azathioprine; Cy: cyclophosphamide; EGPA: eosinophilic granulomatosis with polyangiitis; Haem: haematuria in dipstick; MMF: mycophenolate mofetil; MPO: myeloperoxidase; MTX: methotrexate; N/A: not applicable; NCGN: necrotising crescenteric glomerulonephritis; Pd: prednisolone; PLEX: plasma exchange; PR3: proteinase 3; Prot: protein dipstick; RTX: rituximab; SCr: serum creatinine; TIN: tubulointerstitial nephritis.

CONCLUSION

While renal involvement in EGPA is less frequent than in other ANCA-associated vasculitic (AAV) subgroups, vigilance for its presence is required given its potential to lead to end-organ failure. The literature reports 10% of patients with renal AAV (microscopic polyangiitis/GPA/EGPA) disease are ANCA negative,[1] the authors observed 36% ANCA negative EGPA patients with renal disease. Ureteric stenosis and eosinophilic TIN in this group raises awareness of the non-glomerular and extra-renal manifestations associated with EGPA.[4,7] Necrotising crescentric nephritis was observed in isolation and also with concomitant TIN, opening the dialogue for the possible role of eosinophilic activation for the development of renal disease in EGPA.[4] Furthermore, all patients in this group were ANCA positive, in keeping with previous studies.[9] The predominant specificity, as expected for EGPA, was MPO–ANCA.

Further investigation to assess if ANCA negativity is associated with an eosinophilic infiltrative and granulomatous disorder involving the interstitium and urological tract, while ANCA positivity progresses to a necrotising glomerular disorder typical of all AAV, is of interest. Along with crescentic glomerular disease, tubular interstitial disease as a sole entity can lead to renal injury. Steroid therapy for other manifestations may mask renal disease. The authors draw attention to urological and renal manifestations of EGPA, and the presence of two patients requiring renal transplantation underscores the importance of renal Investigation in EGPA.[10]

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Hungarian Vasculitis Registry: Results of the First Five Years

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Keywords: ANCA-associated vasculitis, Hungarian vasculitis registry, immunosuppression, mortality risk.

Citation: EMJ Nephrol. 2019;7[1]:36-38. Abstract No AR2.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare systemic autoimmune disease with a yearly incidence rate of around 20 in 1million people. This is a challenging disorder causing substantial morbidity and is often life-threatening.[1-6] In order to increase Hungarian nephrologists' vigilance around the disease, and to provide comparative epidemiological and outcome data, the Hungarian Society of Nephrology established the Hungarian Vasculitis Registry in 2013. All Hungarian nephrology centres were asked to participate in data collection of patients with AAV.

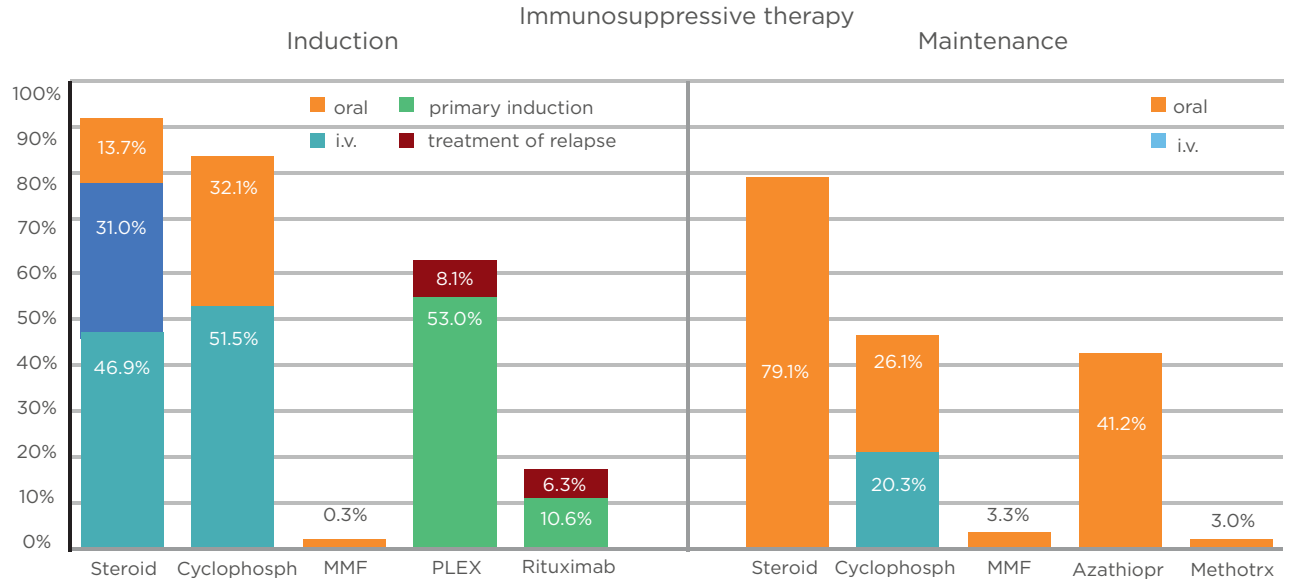

Figure 1: Immunosuppressive therapy for the induction and maintenance of antineutrophil cytoplasmic antibody-associated vasculitis.
Azathiopr: azathioprine; Cyclophosph: cyclophosphamide; i.v.: intravenous; Methotrx: methotrexate; MMF: mycophenolate mofetil; PLEX: plasma exchange.

AIMS AND METHODS

A custom-made web interface was developed for anonymised patient data collection. Clinical and laboratory results, as well as histological renal biopsy results and immunosuppression (ISU) data, were documented. Follow-up data concerning disease activity, remission, relapse, renal function, need for renal replacement therapy, induction and maintenance of ISU, and cause of death were also registered.

RESULTS

Since the interface's initiation, these registry data of 334 patients have been collected. Their mean age was 58.5 years, 64% of which were female. 34% had cytoplasmic type ANCA, 59% perinuclear type ANCA, 2% positivity for both, and 5% proved to be ANCA negative. Renal biopsy showed focal, diffuse crescentic, mixed, and sclerotic histological classes in 28%, 36%, 29%, and 7% of patients, respectively. At baseline, the estimated glomerular filtration rate was 18.5 mL/min, and 31% of the patients required renal replacement therapy (RRT). Following ISU induction, 24% of the initially dialysed patients recovered renal function. Of those who did not need RRT at diagnosis, 15% developed end-stage renal disease during follow-up. Predictors of RRT were diffuse or mixed histology (OR: 10.5, p<0.001; and odds ratio (OR): 3.22, p=0.013, compared to focal, respectively) and the presence of skin lesions (OR: 3.1, p=0.012). Presence of joint involvement seemed to be protective (OR: 0.34, p=0.002). The induction and maintenance ISU are summarised in Figure 1. Remission was achieved in 83% of patients.

During the median follow up of 30 months, 20% of patients died and 6% required transplant. The 1-year, 5-year, and 10-year survival rates were 94%, 82%, and 69%, respectively. Long-term survival appeared better in patients with cytoplasmic type ANCA compared to perinuclear type ANCA positive patients, but this difference disappeared by correcting for age. Predictors of death were age (hazard ratio [HR]: 1.86, p<0.001, for 10 years increment) and requirement of dialysis (HR: 2.98, p<0.001). Female sex (HR: 0.52, p=0.024) and steroid maintenance therapy (HR: 0.37, p=0.003) were protective factors. Relapse developed in 29% of patients, with risk decreasing by age (OR: 0.74, p=0.001), and plasma exchange as part of ISU induction (OR: 0.54, p=0.019). The risk of relapse was higher with lower respiratory symptoms (OR: 1.73, p=0.038).

DISCUSSION

As reflected by the increasing number of yearly reported patients, the Hungarian Vasculitis Registry helps growing nephrologists' awareness of this rare disease and also provides opportunity for quality control. The documented epidemiological and clinical characteristics are comparable to other countries' registry data, and underline the importance of early diagnosis to achieve the best outcome for patients.

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Allo-Haemodialysis as a Novel Renal Replacement Modality: Urea Kinetics in a Paediatric Use Case

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Keywords: Allo-haemodialysis (Allo-HD), haemodialysis, mathematical modelling, urea kinetics.

Citation: EMJ Nephrol. 2019;7[1]:38-39. Abstract No AR3.

BACKGROUND

Lackofaffordablerenalreplacementtherapy(RRT), especially in limited resource settings, puts patients with kidney failure at the risk of imminent death. Globally, between 2.2 and 7.1 million patients may have died prematurely in 2010 because they did not have access to RRT.[1] The authors of the recently published Global Kidney Health Atlas projected that in 2030, 14.5 million people will have end stage kidney disease and need RRT, yet only 5.4 million will receive it because of economic, social, and political factors.[2]

METHOD

The authors propose allo-haemodialysis (alloHD) as a novel dialytic RRT modality. With alloHD, the patient's blood flows in the dialyser counter-current to the blood of a healthy subject ('buddy'). Fluid and toxins transferred from the patient to the buddy are excreted by the buddy's healthy kidneys (Figure 1A).

To quantify the alloHD efficacy, the authors used a two-compartmental model of urea for the patient and buddy. The buddy model also accounts for increased diuresis due to the transferred fluid and urea. The fluid and urea transfer across the hollow fibre is represented by a spatiotemporal model,[3] in which the urea concentration in the patient's blood decreases along the hollow fibre while it increases in buddy's blood, which is flowing in the counter-current direction in the space that is the classical dialysate compartment.

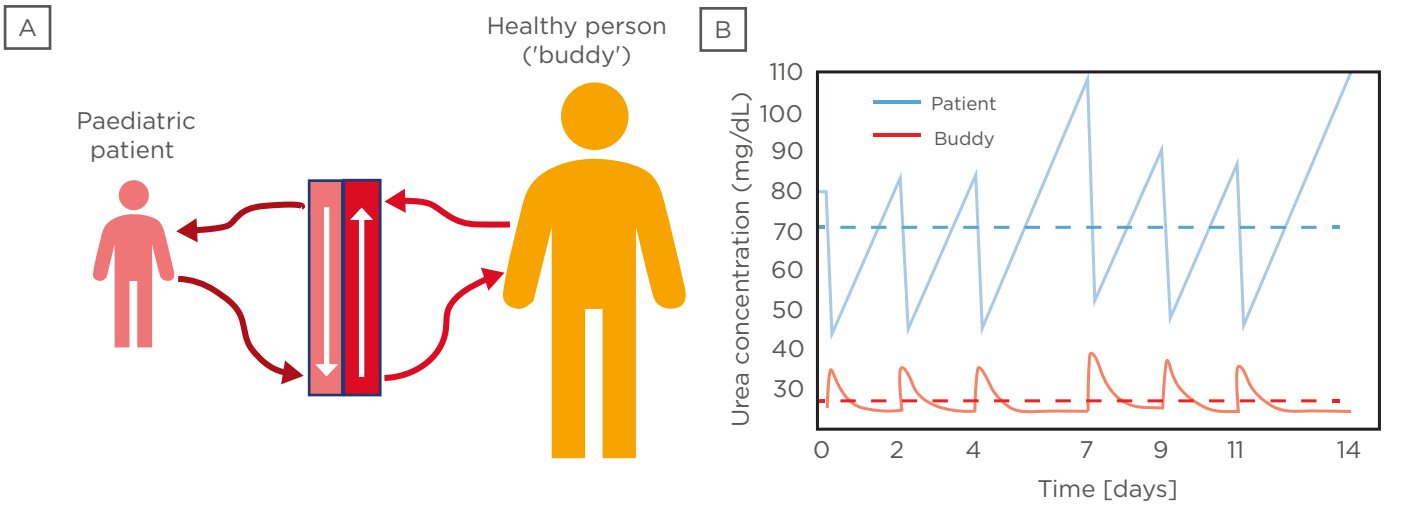

Figure 1: Allo-Haemodialysis in a paediatric patient and adult 'buddy'.

A) Allo-haemodialysis setup in which a paediatric patient (left) is dialysed against a healthy subject (buddy; right). B) Urea kinetics in a paediatric patient (blue) and healthy adult buddy (red). Solid lines correspond to intra and inter-dialytic urea levels; the dashed lines denote time-averaged urea concentrations for both patient and buddy, respectively.

In the analysis, a scenario in which a 20 kg paediatric patient is dialysed against a 70 kg buddy was simulated. The authors use the developed model to assess the long-term urea kinetics in both subjects using a paediatric dialyser (surface area 0.9 m^2), blood flow rates of 150 mL/min, an ultrafiltration volume of 1 L/session, a dialysis time of 4 hours, and a thrice weekly alloHD schedule.

RESULTS

Urea kinetics for an initial urea concentration of 80 mg/dL (patient) and 25 mg/dL (buddy), respectively, were computed. The results suggest that three alloHD sessions per week are enough to keep the patient's time-averaged urea concentration below the initial urea concentration and achieve a weekly standard Kt/V between 1.57 and 1.70 (Figure 1B).

CONCLUSION

While this analysis is limited to urea, other toxins will also be transferred from the patient to the buddy. Further *ex vivo* and animal studies are required to gain further insights into this novel RRT concept.

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Kt/V Achievement and Mortality in Haemodialysis Patients in the Gulf Cooperation Council (GCC) Countries: Results from DOPPS (2012-2018)

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Keywords: Attributable fraction, dialysis adequacy, GCC, haemodialysis (HD), Kt/V, mortality, sex.

Citation: EMJ Nephrol. 2019;7[1]:40-41. Abstract No AR4.

INTRODUCTION AND AIMS

Adequate dialysis, as measured by Kt/V, is important for maintaining good health in haemodialysis (HD) patients. Guidelines recommend single pool Kt/V >1.2 as the minimum dose for thrice weekly HD.[1] Despite a high regional prevalence of risk factors for chronic kidney disease and having a growing dialysis population,[2] little is known about dialysis adequacy in the Gulf Cooperation Council (GCC) countries of Bahrain, Kuwait, Oman, Qatar, Saudi Arabia (KSA), and United Arab Emirates (UAE). Utilising data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) from 2012–2018, this presentation describes: (1) a prevalence of low Kt/V (<1.2) in GCC countries compared to other international regions; (2) predictors of low Kt/V; (3) a relationship between low Kt/V and mortality; and (4) a percentage of low Kt/V cases attributed to treatment time (TT) and blood flow rate (BFR) in different patient subgroups.

METHODS

Data were acquired from initial cross-sections of the DOPPS 5 (2012–2015) and 6 (2015–2018) HD patients (N=1,544) on dialysis >180 days at 40 randomly selected GCC HD units. Country-level results were weighted for the sampling fraction in each unit. Logistic regression was used to estimate the proportion of low Kt/V cases attributable to various treatment practices, and multivariable Cox regression was used to estimate hazard ratios (HR) for low Kt/V on all-cause mortality with adjustments for numerous patient characteristics.

RESULTS

GCC HD patients had a mean age of 55 years, 41% were female, and there was a median dialysis vintage of 2.7 years. Mean BMI was lower for men compared to women (26.1 versus 27.5), but mean body surface area was higher for men compared to women (1.80 m^2 versus 1.67 m^2). GCC HD patients had the highest proportion of patients with single pool Kt/V <1.2 (34% versus 14%, 13%, 9%, and 5%

in Canada, Japan, Europe, and USA, respectively). Kt/V was <1.2 in 27% of GCC females, versus 39% in GCC males. In multivariable logistic models, low Kt/V was more commonly associated ($p<0.05$) with larger body weight and height, male sex, lower TT, lower BFR, greater comorbidity burden, and use of HD as opposed to haemodiafiltration. BFR <350 mL/min and TT <4 hours were common (80% and 43% of patients, respectively). Men had higher mean BFR than women (306 mL/min versus 293 mL/min), and were less likely to have BFR <300 (25% versus 34%). In GCC patients, low Kt/V <1.2 was strongly related to higher mortality in women (HR: 1.86; 95% confidence interval [CI]: 1.11–3.14), whereas a weak mortality association was seen in men. If TT is increased to 4 hours and BFR is increased to 350, the proportion of low Kt/V would fall by 43% among patients with either low TT or BFR, and by 41% in all patients. Among females, 52% of all low Kt/V cases would increase to a Kt/V ≥1.2 if both TT and BFR were increased to target levels, while among males, only 36% of all low Kt/V cases would increase to a Kt/V ≥1.2.

CONCLUSIONS

Mean Kt/V was lower for GCC patients than all other DOPPS regions, with males displaying lower mean Kt/V than females in all areas. Low Kt/V appears related in part to short TT and low BFR, and may increase mortality rates, especially in females. Increasing BFR to 350 mL/min and TT to 4 hours thrice weekly in HD patients will improve Kt/V values and may further improve survival in the GCC, particularly for female HD patients.

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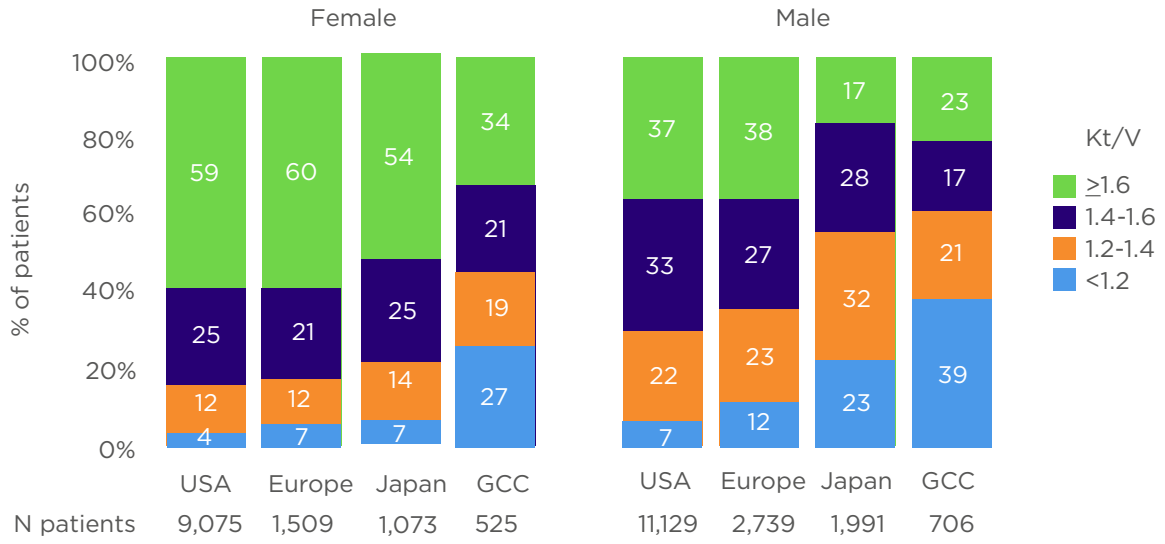

Figure 1: International comparison of Kt/V

Restricted to initial sample of patients at start of DOPPS 5 and 6, representing a prevalent cross-section. Countries included from Europe are Belgium, Germany, Italy, Spain, Sweden, and the UK.
GCC: Gulf Cooperation Council; UK: United Kingdom; USA: United States of America.

Changes in Intraocular Pressure During Haemodialysis and the Role of Ultrafiltration Rate

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Keywords: Haemodialysis, intraocular pressure, ultrafiltration.

Citation: EMJ Nephrol. 2019;7[1]:42-43. Abstract No AR5.

Ocular problems have been reported to exist in patients with end-stage renal disease (ESRD). Discounting ageing itself, which is a known risk factor for glaucoma, older patients with ESRD on haemodialysis (HD) are more likely to have glaucoma. Intraocular pressure (IOP) is a major risk factor for the development and progression of glaucomatous disease, and transient changes in IOP have been reported during HD in patients. This topic is controversial in the literature; whereas elevated IOP is reported in most of the studies as a risk factor for glaucoma development and progression, some results have shown no changes or a decrease in IOP during an HD session. A possible hypothesis that explains the serious increase of IOP during HD involves a potential connection with the rapid decrease in serum osmolarity during dialysis, resulting in an osmotic gradient between the plasma and intraocular fluids due to the presence of the blood-ocular barrier, which can draw water from the plasma into the eye. In eyes that have an obstructed aqueous outflow pathway, it is not possible to have a good aqueous humour drainage, which results in IOP elevation. In addition, it was suggested that the change in IOP during HD correlated with the change in plasma colloid osmotic pressure and bodyweight.[1]

This cross-sectional study was designed to evaluate the effects of one session of HD on IOP and its relationship with ultrafiltration rate. The authors' population consisted of 67 patients, 35% of which were female, with a mean age of 53.2±11.5 years and who were under conventional intermittent HD for at least 3 months. Patients receiving glaucoma treatment, with corneal abnormalities, history of corneal surgery, allergy to topical anaesthetic agents, or a current eye infection, were excluded. Measurements were made at two time points, using a pneumotonometer with the patient in a seated position: approximately 15 minutes before starting HD (T1), and approximately 15 minutes after ending HD (T2).[2] Pre-HD and post-HD plasma osmolarity were also analysed. Plasma osmolarity was calculated as: plasma osmolarity = 2(Na) + [(glucose)/18] + [(SUN)/2.8], where Na indicates plasma sodium ion concentration (mMol/L), glucose indicates plasma glucose concentration (mg/dL), and SUN indicates levels of serum urea nitrogen (mg/dL). The authors multiplied by 0.0555 and 0.3570, respectively, to convert glucose and SUN to mMol/L.[2]

Blood pressures were also measured at these times. In addition, ultrafiltration rate was calculated for each patient. Echocardiographic studies were performed prior to and 30–60 minutes following the dialysis session. Mean inferior vena cava diameter (IVCD) was expressed as (IVCD in inspiration + IVCD in expiration)/2. IVCD was adjusted for body surface area.

During evaluation, the authors found that laterality of the eyes (right or left) had no significant effect on the pre-dialysis and post dialysis IOP values. Significant increases in IOP and decreases in plasma osmolarity, systolic blood pressure, and IVCD were found post-dialysis session ($p<0.012$, $p<0.034$, $p<0.39$, and $p<0.45$, respectively). Changes in the IOP correlated with ultrafiltration rate (correlation coefficient [r]=-0.5; $p<0.01$) and differences in IVCD ($r=0.4$; $p<0.01$). However, there was no significant correlation between changes in IOP and plasma osmolarity ($r=-0.2$; $p>0.2$).

In conclusion, these results indicate a relationship between HD, ultrafiltration rate, and IOP in ESRD patients. Higher ultrafiltration rate may predict increased risk for glaucoma in HD patients so scheduled ophthalmic examination should be a

regular protocol for HD management. For patients evaluated to be at a high risk, longer or more frequent dialysis sessions should be considered to prevent the deleterious consequences of excessive body fluid expansion.

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Changes of Salivary Creatinine and Urea in Animal Models of Kidney Disease

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Keywords: Creatinine, home monitoring, non-invasive markers, renal failure, saliva, salivary urea nitrogen (SUN).

Citation: EMJ Nephrol. 2019;7[1]:43-44. Abstract No AR6.

BACKGROUND

Plasma creatinine and urea are widely used as markers of renal function. Saliva is an alternative diagnostic fluid with many advantages in comparison to blood; it is easier and cheaper as collection does not require trained staff and it offers the possibility to repeat the non-invasive sample collection if needed. Both creatinine and urea can be measured in saliva, but the biological variability is high, and its determinants are unknown. Animal models and experiments under controlled conditions are needed, but they are scarce. In addition, the association between salivary and plasma concentrations of creatinine and urea in different stages of renal failure is not clear. The aim of this study was to investigate the dynamics of salivary markers of renal function during the progression of acute and chronic kidney disease in animal models.

METHODS

In the study, 90 adult, male Wistar rats underwent either bilateral nephrectomy (BNX), ischaemic-reperfusion injury (IRI), or glycerol nephropathy (GLY) to induce acute kidney injury (AKI), or 5/6 nephrectomy to induce chronic kidney disease (CKD). Blood and saliva samples were collected at baseline and at 3, 6, 12, and 24 hours after AKI induction or at baseline, and 2, 4, and 6 months after CKD induction. Creatinine and urea were assessed using standard spectrophotometric methods.

RESULTS

Plasma urea saw increases 3 hours after AKI induction in BNX (by 40%; $p<0.010$) and IRI (50%; $p<0.001$), while salivary urea was 2-times higher ($p<0.001$) but was seen 9 hours later. In BNX and IRI models, plasma creatinine was elevated after 12 hours (by 180%; $p<0.001$, and by 200%; $p<0.001$, respectively) followed by an increase in saliva after 24 hours (by 300%; $p<0.01$, and 160%; $p<0.05$, respectively). In GLY, the dynamics of urea was similar in plasma and saliva (by 130%; $p<0.01$, and by >100%; $p<0.05$, respectively), in contrast, creatinine in plasma,

but not in saliva, increased after 48 hours (by 180%; p<0.05, and p=0.53). The 5/6 nephrectomy led to higher plasma and salivary urea after 2 months (by 50%; p<0.001, and 40%; p<0.01), while plasma, but not salivary creatinine was higher after 6 months (by 60%; p<0.001, and p=0.99, respectively).

DISCUSSION

This is the first study to analyse the detailed dynamics of salivary creatinine and urea in renal failure. The analysed markers in saliva followed their increase in plasma with a considerable delay in both AKI and CKD models. Further studies are needed to evaluate whether this time delay can be outweighed by the diagnostic advantages of saliva in real-life screening or monitoring of kidney diseases.

Impact of Chronic Kidney Disease on the Drugs Eliminated Predominantly Through a Non-Renal Route: A Proof of Concept Study with Citalopram

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Citalopram, non-renal clearance, pharmacokinetics.

Citation: EMJ Nephrol. 2019;7[1]:44-46. Abstract No AR7.

INTRODUCTION

Drug dosing in patients with chronic kidney disease (CKD) can be challenging due to the exclusion of such patients in the clinical trials during the drug development process. It is increasingly evident that CKD can affect the elimination of drugs excreted not only by the renal route, but also through non-renal routes (bile, gut) and through metabolism (liver).[1] The uremic toxins generated in CKD can affect the clearance of drugs by a multitude of mechanisms, including alteration in the function of hepatic drug metabolising enzymes.[2] Citalopram is an antidepressant drug eliminated predominantly (85%) by cytochrome p450 enzyme (CYP2C19 and CYP 3A4)-mediated hepatic metabolism.

This study aimed to demonstrate the impact of CKD on the hepatic clearance of citalopram by correlating the citalopram concentration in patients with various stages of CKD and modelling hepatic clearance of citalopram with declining CKD.

METHODS

The study was conducted on 75 patients who were on regular citalopram within the Salford Kidney Study (total patient population: 3,115) between October 2002 and December 2016. One hundred and fifty citalopram levels were assayed for analysis from the available baseline and annual follow-up samples of these 75 patients by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The patients were grouped into moderate (CKD stages 2 and 3) and severe CKD (CKD stages 4 and 5) based on their estimated glomerular filtration rate (eGFR). Pearson's correlation analysis was used to correlate the citalopram concentrations with

eGFR in SPSS. A single compartmental population pharmacokinetic model was generated using standard citalopram pharmacokinetic parameters and applied to compare the trend in hepatic clearance of the drug across various CKD stages using Monolix software (version 2018R1; Lixoft, Paris, France). Forty-three patients with two or more levels were used in this pharmacokinetic trend analysis.

RESULTS

The median age of the cohort was 65 years with a predominance of females (56%) and Caucasians (100%). Median eGFR of the population was 30.5 mL/minute/1.73 m^2. The median dose-adjusted citalopram concentration was observed to be significantly higher in the severe CKD patient group (6.65 versus 3.78 ng/mL/g; p<0.001). In the Pearson's correlation analysis there was a significant negative relationship between eGFR and the dose-adjusted citalopram levels (correlation coefficient [148] : -29; p<0.001) and this significance extended in the partial correlation analysis after controlling for other important confounding variables. In the population pharmacokinetic model, a 23% reduction in the mean hepatic clearance was noted in the severe CKD group compared to the moderate CKD group, which was statistically significant (p<0.001) (Figure 1). A reduction in hepatic clearance was also noted in females, patients of an older age, and those taking proton pump inhibitor tablets, a finding which is supported in previous literature.[3,4]

CONCLUSION

The study results support the hypothesis that metabolism of drugs eliminated predominantly by the non-renal route (hepatic metabolism) can be reduced with advancing CKD, possibly due to inhibition of the hepatic drug metabolising enzyme activity by uraemic toxins. Further prospective studies are warranted to delineate these differences and aid dosing in advanced CKD.

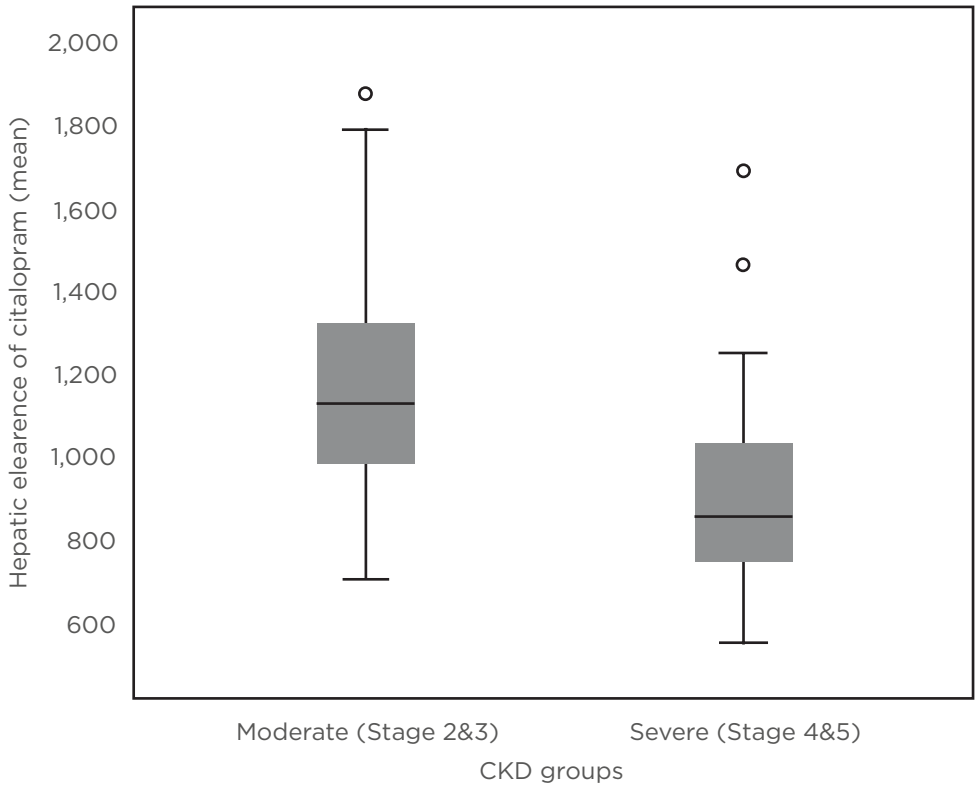

Figure 1: Mean hepatic clearance of citalopram in the moderate and severe chronic kidney disease groups.

CKD: chronic kidney disease.

Following the presentation of these results at the European Renal Association-European Dialysis and Transplant Association 2019 Congress, discussions were focussed around the clinical implications of the project and how models can be useful in precision drug dosing in this special group population in the future

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A Novel Mechanism of Diclofenac's Action: Inhibition of Kynurenic Acid Production in Rat Kidney *In Vitro*

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Keywords: Diclofenac, kidney, kynurenic acid, nephrotoxicity, non-steroidal anti-inflammatory drugs, rat.

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Non-steroidal anti-inflammatory drugs (NSAID) are one of the most popular analgesics due to their efficacy and availability over the counter.[1] However, there are increasing safety concerns about NSAID side effects.[2] Inhibition of prostaglandin synthesis within the kidney, which impairs renal perfusion, is the main mechanism of NSAID-induced nephrotoxicity.[3] Diclofenac, a prominent NSAID, is claimed to evoke kidney damage even in patients without previous renal dysfunction.[4] Experimental data suggest that the mechanism of diclofenac's action may go beyond cyclo-oxygenases inhibition in a way that is responsible for the drug's toxicity.[5]

Overactive glutamate signalling in the kidney leads to renal pathologies, and as such glutamate receptor antagonists are claimed to be nephroprotective;[6] however, results of other studies remain controversial.[7] Kynurenic acid (KYNA), a metabolite of tryptophan, is synthesised from L-kynurenine by kynurenine aminotransferases (KAT).[8] KAT I and KAT II isoenzymes are the most studied KAT isoforms.[9] The main mechanism of KYNA action is nonselective antagonism towards ionotropic glutamatergic receptors, especially N-methyl-D-aspartate types, which are predominantly expressed in the kidney. Natriuretic, anti-inflammatory, and hypotensive properties of KYNA are well established.[10]

The aim of this study was to examine the effect of diclofenac, one of the strongest and most commonly prescribed NSAID, on KYNA formation and the activity of KAT I and KAT II, in rat kidney *in vitro*. Furthermore, the molecular docking of diclofenac to KAT I and KAT II structures was conducted to study the mechanism of drug-enzyme interaction. This was followed by microarray data mining to investigate whether

diclofenac can affect the expression of KAT-coding genes.

Diclofenac at 500 µM and 1 mM lowered KYNA formation in kidney homogenates *in vitro* to 67% ($p<0.001$) and 36% ($p<0.001$) of control value, respectively. At 500 µM and 1 mM concentration, diclofenac decreased renal KAT I activity *in vitro* to 40% ($p<0.05$) and 41% ($p<0.01$) of control value, respectively. Additionally, diclofenac at 50 µM, 100 µM, 500 µM, and 1 mM concentration decreased kidney KAT II activity *in vitro* to 88% ($p<0.01$), 62% ($p<0.01$), 11% ($p<0.01$), and 4% ($p<0.01$) of control value, respectively. Molecular docking results suggested that diclofenac may interact with the active site of KAT I and KAT II. Publicly available microarray datasets suggested that diclofenac does not affect the expression of KAT-coding genes.

To summarise, diclofenac decreases KYNA production in rat kidney *in vitro* by inhibiting KAT I and KAT II isoenzymes. Results of this study show a novel mechanism of diclofenac action in the kidney. Its relation to drug induced nephrotoxicity should be clarified in future studies.

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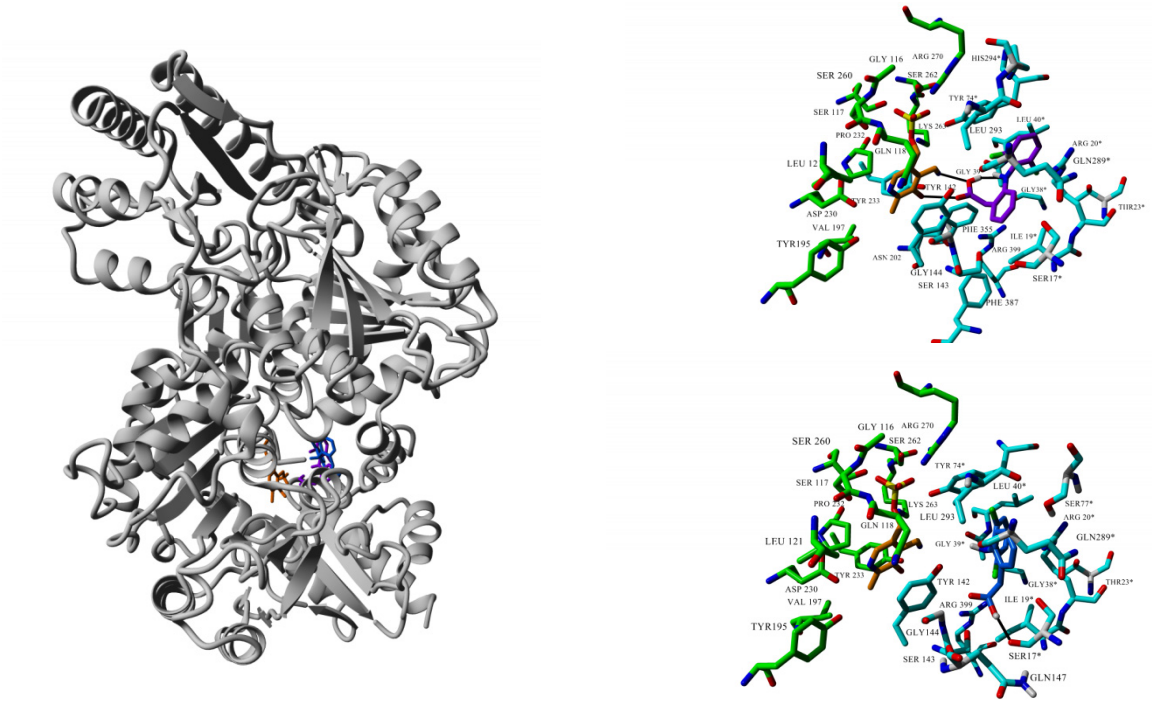

Figure 1: Molecular docking of diclofenac (two orientations: purple and blue) to the crystal structure of KAT II (PDB ID: 2R2N). Ligand and co-factor PMP (orange) are rendered in stick mode, residues involved in ligand and PMP binding are shown in cyan and green, respectively.

KAT II: kynurenine aminotransferase II; PMP: pentamannosyl 6-phosphate.

NephMadness: Lessons from Seven Years on the Leading Edge of Social Media Medical Education

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Keywords: Kidney disease, kidney week, NephMadness, nephrology, social media, twitter.

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BACKGROUND

Metcalfe's Law states that the value of a network is proportional to the square of the number of connected users.[1] So, networks with few users provide low value and each additional user increases the value of the network exponentially. This law makes it particularly difficult for newer, smaller networks to grow because they are low value due to their low population. At the beginning of the decade (circa 2010), nephrology social media was a new, small network. At that time, a core group of bloggers envisioned a large network of engaged and academically minded nephrologists participating in an active, multifaceted, always-on conversation to provide support, answer questions, discuss journal articles, and share resources. To promote this vision and entice nephrologists to participate, they presented at hospital-wide grand rounds, resident teaching rounds, and national meetings.[2] Convincing individuals to sign up for a social media account with the intention of professional use was difficult, but even if a person successfully signed up to Twitter, new users would not know what to do, where to look for like-minded nephrologists, or how to engage with peers. Beyond the issue of how to use social media was the fundamental problem that the value proposition of the nephrology social network was low due to its limited size and activity.

An example of the early growth and challenges to building a self-sustaining network of connected

nephrologists is the American Society of Nephrology's (ASN) Kidney Week. Kidney Week is the largest annual meeting of nephrologists from around the world. The growth of Twitter use at Kidney Week every year was steady and it was consistently the busiest time in the nascent nephrology social media community.[3] During the conference a flood of nephrologists participated in Twitter. They commented on speakers, promoted their talks, shared pictures of posters, and planned where to get dinner. ASN was a willing partner and made changes to their conference to promote social media. Changes included stopping the ban on photography during presentations and changing the official hashtag from KidneyWk plus the year (e.g., #KidneyWk12, #KidneyWk13) to just #KidneyWk in 2015 to preserve those two characters for the message in a character-limited Twitter post.[4,5] However, despite the dramatic Twitter activity during Kidney Week, few of these participants remained in the social media space after the meeting ended. During the conference the network grew in size so that it was highly valuable to participants, but after the conference, use and participation in the network returned to its low, pre-conference state.

To add value to the nephrology social media network, an ethos emerged that content provided on social networks would be accurate, referenced, and open access. This content is labelled free open access medical education (FOAMed) and is a hallmark of medical social media and is not unique to the nephrology sphere.[6-9]

The core organisers of what was to become NephMadness wanted to create an event to drive individuals to participate in the nephrology social media space. The core question was "Could the enthusiasm of Kidney Week be replicated and sustained to create a persistent, rich, supportive community in social media without an actual conference?"[10]

ORIGIN STORY

In 2012, Andrew Levey, then Editor in Chief of the American Journal of Kidney Diseases (AJKD), the scientific journal of the National Kidney Foundation (NKF), wanted to engage social media to support the journal. He picked Dr Kenar Jhaveri to create eAJKD, an academic blog, and Dr Jhaveri added several other medical educators using blogs to participate. Among this cohort was Dr Matt Sparks, who was leading the collaborative blog, Renal Fellow Network[11] and Dr Joel Topf who was running his personal blog, Precious Bodily Fluids. eAJKD, whose name would later change to AJKD blog, published commentaries about original investigations in the journal as well as interviews with the authors about their research. It built a steady readership and became an important player in the nephrology blogosphere.[12]

In February 2013, Drs Jhaveri, Sparks, and Topf discussed how the blog should recognise World Kidney Day and National Kidney Month. Dr Topf proposed a campaign wherein the blog produced a facsimile of the NCAA college basketball tournament that occurs every March: March Madness. The central element of this tournament are the 'brackets', a graphical representation of the single elimination tournament. The proposal, NephMadness, was to create the nephrology equivalent of the tournament with 64 nephrology concepts or 'teams' arranged in a similar bracket. Fans of the basketball tournament try to predict the outcomes of all 63 games in the tournament by "filling out their brackets".[13] NephMadness would offer the nephrology community the same opportunity of predicting the outcomes of this entirely hypothetical tournament of nephrology concepts. The organisers hoped that the NephMadness promotion would pierce the social media bubble and reach a wider community beyond the limited audience of nephrologists already engaged in social media.

To help participants make educated picks for NephMadness, the organisers provided original, fully-referenced, and illustrated descriptions of each concept. These descriptions are called 'Scouting Reports'. The scouting reports covering all 64 concepts from the first year were >12,000 words long and stretched across 9 posts on the AJKD blog.[14] This FOAMed is the primary educational content of NephMadness.

That first year, the tournament was largely produced by Drs Topf and Sparks with help from the other writers on the AJKD blog. The hashtag #NephMadness was used by 77 people in 2013, across 484 tweets during the month-long game. To put those numbers in perspective, 4 months

prior, #KidneyWk12 was tweeted 1,283 times by 268 people.

As a result of this positive reception, plans were made to continue the tournament in 2014. Each year a new logo has been designed to help promote and identify the tournament (Figure 1).

RINSE, WASH, REPEAT, IMPROVE

The lasting observation from the first year of NephMadness was 'potential'. Each year after the first iteration, the NephMadness team has attempted to enhance the programme (Table 1). Two innovations for the second year were instrumental to the success of the project:

1. Online submission of brackets
2. Recruitment of experts to help craft the brackets

During the first year, there was no way for participants to formally enter and record their entries. The second year, the organisers used Tourneytopia, a company that provides white-labeled, web-based software for running tournaments like March Madness.[15] This software allowed the organisers to automatically track and score entries, declare a winner, and provide instant email communication announcing each round of results.

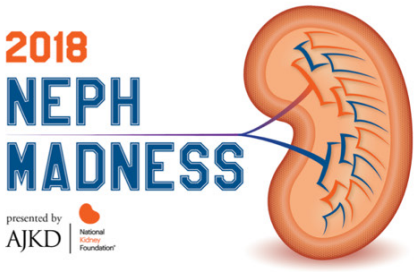
2013: Matt Sparks

2014: Adam Underwood

2015: Adam Underwood

2016: Adam Underwood

2017: Adam Underwood



2018: Peter Dong

2019: Peter Dong

Figure 1: The NephMadness logos with the name of their designer.

Table 1: Participation on Twitter and in the contest itself from origin through to 2020, including a timeline of the innovations in the project.

Year	Tweeters/tweets	Submitted a bracket	Major innovations
2013	77/484	N/A	The Tournament, Logo, Hashtag
2014	154/1,408	256	Professional Logo, Tourneytopia, Selection Committee
2015	382/4,085	342	Blue Ribbon Panel, NephMadness in a Box, Collaboration with Medscape
2016	486/4,521	498	Field of 32, #BlueRibbonFail
2017	782/6,615	736	Quinlan videos, Dr Timothy Yau
2018	1,139/7,979	989	Dr Anna Burgner, NephMadness Twitter Account, CME, Group Participation
2019	1,719/8,355	1,393	Podcasts, Instagram, Parties, MOC
2020	TBD	TBD	Dr Samira Farouk

The other innovation was the development of the selection committee. In March Madness, every conference champion gets a bid to go to the tournament. Those champions represent roughly half the field, and the remaining teams are chosen by a selection committee of basketball experts. In NephMadness, the executive team selects the academic regions with input from the community, and then taps an expert on the topic to select the specific concepts to represent the region; these experts are the NephMadness selection committee. The selection committee not only provides expertise, but they also lend credibility to the contest. One of the recurring problems with online medical education is providing credibility.[16] Since the platform is inherently democratic, anyone can publish medical information without the checks and editing that mark traditional journal-based, peer-reviewed publications. Doctors are naturally suspicious of this.[17] By bringing in well-known thought-leaders, NephMadness was able to diminish this credibility gap. To get high profile experts to work with NephMadness, the executive team does not ask the experts to write the editorial descriptions of the regions. Authors with experience writing for an online audience are brought in to create the blog posts describing the concepts. The selection committee members help to proof and endorse these reports before they are posted online.[18] The writing of the scouting reports is done by the entire NephMadness team.

During the second year the audience roughly doubled, but with the new, online bracket submission and scoring there was a lot more attention on the winners of the hypothetical match-ups. In 2013 and 2014, NephMadness used a combination of majority wins (the concept with the most support won the match-up) and 'Joel and Matt Decide' to determine the winners. This resulted in plenty of participants being upset with the advancing teams and concepts;[19] however, the majority in a poll wanted to continue to use the 'Joel and Matt Decide' method.[20] For 2015, the NephMadness executives instituted a Blue Ribbon Panel to determine the winners of the 63 match-ups in NephMadness. The Blue Ribbon Panel consisted of a hand-picked group of seven educators, editors, and leaders in the field of nephrology who voted on every match-up in the bracket. The Blue Ribbon Panel remains an essential component of the tournament and was expanded to nine members in 2019.

Not every innovation was successful or was planned and implemented by the executive team. In 2015, NephMadness partnered with Medscape. The idea was to leverage the large audience of a general medicine website to increase engagement with NephMadness. This collaboration added complexity to NephMadness as the content appeared on both the Medscape website as well as the AJKD blog. Unfortunately, participation did not increase beyond the organic growth typically seen from year to year. Similarly, NephMadness also partnered with Visible Health

in 2015 to produce a NephMadness iPad and iPhone app to display the NephMadness content.[21] This added complexity to the game but did little to expand the pool of players. Both the iPad app and the collaboration with Medscape were not continued the following years.

The most interesting innovation, at least from the executive committee's perspective, came from the crowd and not the organisers. In 2016, the Blue Ribbon Panel voted that blood pressure control was more important for nephroprotection than for heart protection. The data for cardiovascular protection from blood pressure control is clear and consistent, while blood pressure's role in slowing progressive kidney failure is mixed with no convincing interventional data showing improvement in kidney outcomes from better blood pressure control.[22] Following the announcement of the Blue Ribbon Panel decision, NephMadness participants took to Twitter to complain under the hashtag #BlueRibbonFail. The 'mistake' by the Blue Ribbon Panel sparked controversy and engaged the participants in a way that a correct call never would. The Blue Ribbon published a response justifying their decisions which furthered the online conversation.[23]

SUCCESSION

With 7 years of running the programme, there have been significant changes in the executive and editorial teams responsible for NephMadness. The most significant of these occurred in 2016, when Dr Andrew Levey and his team at Tufts University, Boston, Massachusetts, USA, completed their second 5-year term as editor of AJKD. The editorship shifted to the University of Pennsylvania, Philadelphia, Pennsylvania, USA, under the direction of Dr Harold Feldman.[1] In January 2017, Dr Jhaveri passed the editorship of the AJKD blog to Dr Tim Yau of Washington University in St. Louis, Missouri, USA.[24] As part of his role at AJKD blog, Dr Yau assumed a leadership role in NephMadness. The following year, Dr Anna Burgner of Vanderbilt University, Nashville, Tennessee, USA, was added to the leadership team of NephMadness. Most recently, Samira Farouk, Icahn School of Medicine at Mount Sinai, New York City, New York, USA, has joined the team for 2020.

With new leaders comes new ideas. Dr Burgner spearheaded the addition of Continuing Medical Education (CME) credit to NephMadness.[25] In 2019, American Board of Internal Medicine Maintenance of Certification (MOC) credit was offered.[26] These additions pay dividends, not only in providing credit for people who desire it, but the process of getting the educational materials certified for CME and MOC meant an additional round of critical review of the material, further increasing the quality of the content produced. CME and MOC also provide a signal that this content is reliable, providing additional credibility to the whole concept.

REACH AND CHALLENGES

In 2019, NephMadness had almost 1,400 people fill out brackets from 53 countries. Parties celebrating NephMadness took place on four continents. Over 1,700 people tweeted 8,000 times about the contest. NephMadness partnered with the popular internal medicine podcast, 'The Curbsiders', and recorded four podcasts covering roughly half of the core content of the game. Each of these podcasts was downloaded >30,000 times and 60% of people listened to the entire episode.[27] Traffic to the AJKD blog website was its highest ever and surpassed 1 million views. NephMadness continues to provide an innovative way to create and share nephrology FOAMed.

Despite the apparent success of NephMadness, the concept as currently implemented has some fundamental problems that limit its effectiveness as an ambassador for FOAMed. NephMadness is complex. One significant barrier to participation is the presence of two disparate websites. The NephMadness website at AJKD blog houses all the educational content, but participants must register and fill out their bracket at a separate website, Tourneytopia.

During the first year of NephMadness, 50 pages of editorial content was released all at once. In 2016, the NephMadness field was trimmed from 64 to 32 concepts, but there still were roughly 30 pages of content released at the start of the contest. This initial content is followed by invited editorials by experts providing additional content. For many social media users, this amount of medical educational content can feel overwhelming.

Additionally, just over half of participants in NephMadness are from outside the USA. As more of the participants come from outside the USA, a game based on a USA college basketball tournament makes less sense.

One of the stated goals of NephMadness was to promote engagement on social media and then remain active after the contest finished. Judging from the Twitter participation numbers, NephMadness has succeeded in the former but the latter is difficult to measure. The authors' sense that, like ASN's Kidney Week, many come to social media for the game, but do not continue to participate once the event is completed.

The executive team recognises these challenges and has ideas and innovations that will be trialed in 2020 to continue to make NephMadness even better. With these innovations, they hope to inspire NephMadness participants to not just play the game, but to stick around the rest of the year, engaging with the nephrology social media community and exponentially increase the value of the network and discussions online.

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Renal Regeneration: Stem Cell-Based Therapies to Battle Kidney Disease

EDITOR'S PICK

Transplant organ shortage remains a major issue for nephrologists around the globe. In this article, Morizane et al. provide an excellent overview of the current usage of stem cells to combat kidney disease and thus presents a potential solution to this important issue.

Dr Angela Yee-Moon Wang

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Abstract

While the worldwide prevalence of kidney disease is increasing rapidly, the current therapeutic repertoire for these patients is often limited to dialysis and organ transplantation. However, advances in developmental and stem cell biology have highlighted the potential of stem cells for the development of novel renal regeneration therapies. While there are currently no approved stem cell-based treatments for kidney disease, various types of stem cells have been shown to facilitate regeneration of kidney tissue in preclinical models of both acute and chronic kidney injury. This review summarises the current status of stem cell-based therapies to battle kidney disease. In addition, future directions

for the clinical translation of stem cell research towards development of novel renal regeneration therapies are discussed.

INTRODUCTION

Organ shortage continues to be the major unresolved problem in transplantation medicine. Although organ transplantation is currently the best treatment to repair organs and tissues that have lost their native function, stem cell-based therapies provide promising alternatives to counteract the shortage of donor organs.[1,2] Since the introduction of haematopoietic stem cell transplantation,[3] scientific insights into cell-based therapies are gradually finding their way to the clinic and into the patient.[4] In recent years, the number of cell-based clinical trials using somatic stem cells or derivatives of pluripotent stem cells (PSC) has markedly increased.[4-6] PSC, including embryonic stem cells and induced PSC (iPSC), are expected to be the most promising cell source within the field of regenerative medicine due to their prolonged proliferative potential and multilineage differentiative capacity. Furthermore, human iPSC (hiPSC) can be readily generated from patients, which provide possibilities to develop immunocompatible tissues tailored not only to a specific disease, but also to an individual patient. Recently, several clinical trials have been performed, including those on the topic of transplantation of oligodendrocyte progenitor cells in patients with spinal cord injury,[7] transplantation of encapsulated beta cells to battle Type I diabetes mellitus,[8] treatment of age-related macular degeneration using retinal pigment epithelium cells,[9-11] and transplantation of mesenchymal stem cells (MSC) in patients with graft-versus-host disease (GVHD).[12] Additionally, clinical iPSC research is also set to begin for patients with myocardial infarction and Parkinson's disease in Japan.[13]

In the field of kidney disease, stem cell-based therapies are the centre of attention for treatment of chronic conditions leading to irreversible kidney failure. Chronic kidney disease (CKD) affects up to 13.4% of the population worldwide and is associated with a serious financial burden, making it a growing public health and economic concern.[14] CKD is characterised by gradual, irreversible loss of nephrons, the functional units within the kidney, before eventually progressing towards end-stage renal disease. In turn, patients with end-stage renal disease are dependent on renal replacement therapy, including kidney transplantation or haemodialysis, for survival. However, kidney transplantation has been limited by a shortage of donor kidneys, whereas haemodialysis requires high costs relative to the increase in quality of life and average life expectancy. In this scenario, stem cell-based therapies bear the potential to overcome the above-mentioned limitations, providing not only a cost-effective, but also a long-term treatment option for patients with CKD. For kidney disease, three major strategies for stem cell-based therapies have been proposed (Figure 1). The first strategy takes advantage of the anti-fibrotic, anti-inflammatory, and angiogenic potency of MSC, while the second strategy focusses on the transplantation of kidney-specific progenitor cells differentiated from PSC. The third strategy encompasses the xenotransplantation of animal-derived kidneys. In this review, the current status of these three strategies for stem cell-based therapies to confront kidney failure is summarised. The growing concept of kidney resident stem cells, a pre-existing intratubular stem cell population, also referred to as scattered tubular cells, for kidney regeneration is not included in this review. This cell population has been extensively reviewed elsewhere.[15] In addition, the authors discuss the future directions of stem cell-based therapeutics for kidney diseases and alternatives to circumvent the shortage of donor organs in renal transplantation medicine.

MESENCHYMAL STEM CELLS TO TREAT RENAL DISEASE

MSC, a population of rare progenitor cells, were first identified in bone marrow >50 years ago.[16,17] MSC are a specialised subset of non-haematopoietic cells, defined by capabilities of self-renewal and differentiation into the mesodermal lineage (giving rise to osteogenic, chondrogenic, and adipogenic cells). Some

studies suggested that MSC are also able to differentiate into ectodermal and endodermal lineages,[18-20] yet this pluripotent potential of MSC is still under debate.[21]

Because MSC extracted from bone marrow exhibit heterogeneous characteristics, phenotypic and functional equivalence is required for the use of MSC in any clinical context. The International Society for Cellular Therapy (ISCT) defined three criteria to characterise MSC: 1) MSC must adhere to plastic culture plates under standard tissue culture conditions; 2) MSC should express mesenchymal markers, including CD105, CD73, and CD90, but not haematopoietic markers, such as CD45, CD34, CD14/CD11b, CD79a/CD19, and human leukocyte antigen (HLA)-DR; 3) MSC should have the ability to differentiate into skeletal tissue, osteoblasts, adipocytes, and chondrocytes under *in vitro* conditions.[22]

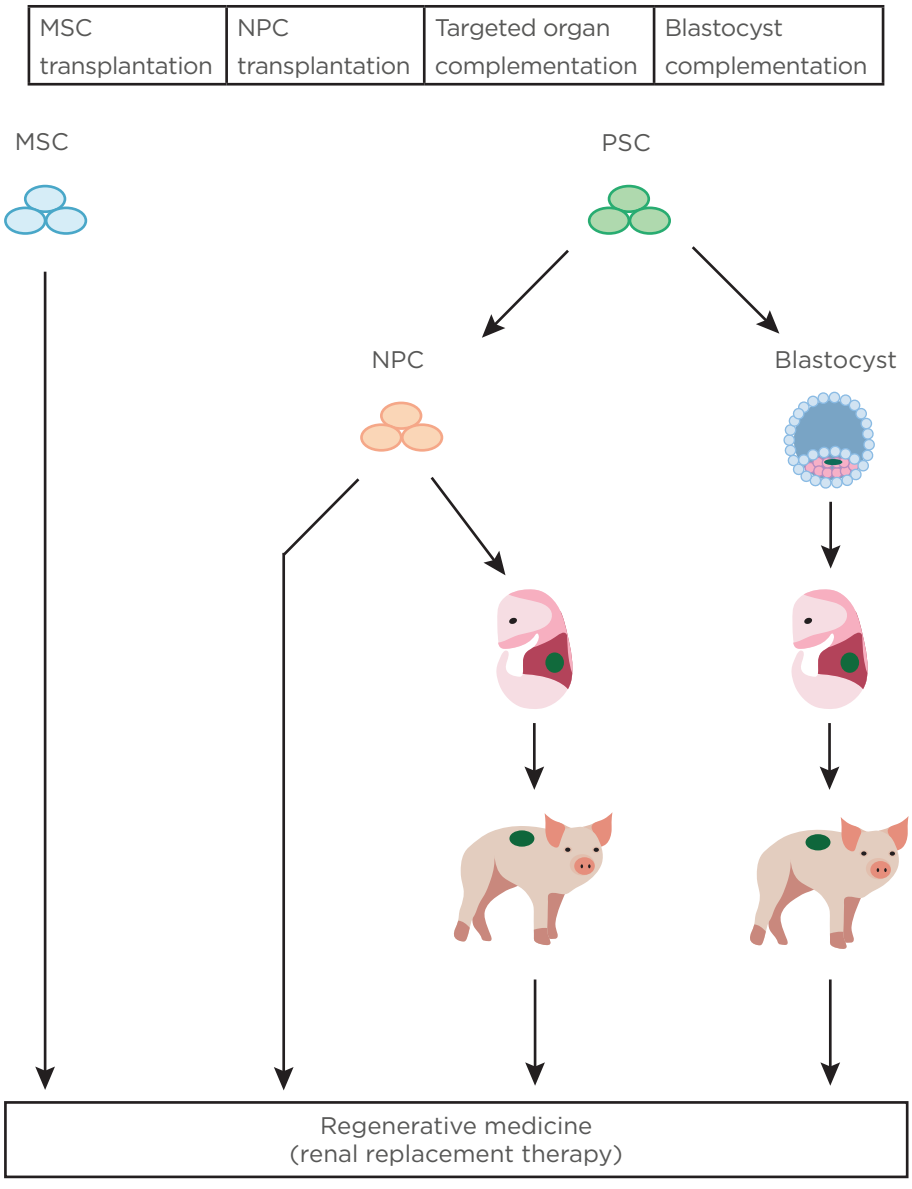

Figure 1: Overview of stem cell-based strategies to treat kidney disease.

Strategies proposed for renal regeneration include the transplantation of mesenchymal stem cells, nephron progenitor cells derived from pluripotent stem cells, and xenotransplantation of animal-derived kidneys following targeted organ or blastocysts complementation.

MSC: mesenchymal stem cells; NPC: nephron progenitor cells; PSC: pluripotent stem cells.

Based on these criteria, MSC have been isolated from a wide variety of fetal and adult tissues, including fetal amniotic fluid, placenta, umbilical cord, adipose tissue, endometrium, bone, kidney, lung, and liver.[23] Of note, comparison of gene expression profiles showed considerable differences in MSC phenotype and functional capacity based on their tissue of origin.[20,24-26]

For therapies using human MSC (hMSC), three distinct mechanisms can be discerned: 1) hMSC differentiate into a variety of cell types, which allow repair or reconstruction of bone tissue and cartilage;[21,27-29] 2) hMSC can modulate the microenvironment surrounding the injured tissue by secretion of immunosuppressive and anti-inflammatory factors that arrest cell cycle progression of invading immune cells, such as B cells, T cells, and macrophages. These immunomodulatory effects can be used to tackle various immune-related diseases, such as acute GVHD and Crohn's disease.[5,30] Finally, 3) hMSC secrete growth factors, cytokines, and extracellular vesicles that stimulate vascularisation and prevent apoptosis and fibrosis. Based on these secretive functions, hMSC are being explored as a cell-based therapy for myocardial injury, liver cirrhosis, and renovascular disease.[31-36]

In the field of kidney disease, several preclinical reports have indicated the therapeutic potential of MSC in animal models of acute kidney injury (AKI) and CKD. In these models, bone marrow and adipose-derived MSC showed protective and regenerative effects via paracrine anti-inflammatory, anti-fibrotic, and vascularisation properties.[37,38] Accordingly, findings from several studies specified the secretion of extracellular vesicles as a major mechanism of action by which MSC can transfer biological cues to promote regenerative processes in injured renal cells.[35-37] In recent years, some clinical studies have investigated the administration of hMSC in patients with AKI and CKD.[39] Saad et al.[34] assessed the safety of intra-arterial treatment with autologous, adipose-derived hMSC in patients with atherosclerotic renovascular disease. Single infusion of hMSC (1.0×10^5 or 2.5×10^5 cells/kg) increased cortical perfusion and renal blood flow, and reduced renal tissue hypoxia, suggesting a potential adjunctive role for hMSC in the management of ischaemic renal disease.[34]

On the contrary, intra-aortic delivery of hMSC in 156 adult subjects with early-stage AKI who were undergoing cardiac surgery showed no beneficial effects.[40] There are several reports that the mechanism of renal repair observed following ischaemia-reperfusion injury does not include replacement of renal tubule cells by injected hMSC.[41-44] Instead, cytokines secreted by hMSC exert transient immunosuppressive and regenerative effects, such as increased angiogenesis.[34] This would suggest that besides hMSC, other stem cell or progenitor-like cells are necessary to restore kidney tissue. As the regenerative potential of hMSC for kidney disease remains controversial, more clinical evidence is needed to pinpoint the use of hMSC as a treatment for kidney disease.

To establish an effective and stable hMSC-based therapy, several challenges are still looming. The function of hMSC is known to decline with age, as the culture expansion needed before hMSC transplantation is associated with cellular senescence. Therefore, recommendations for the clinical use of hMSC are restricted to 3–5 passages.[45,46] In a Phase II clinical trial, Le Blanc et al. showed that infusion of early-passage hMSC into patients with GVHD resulted in a better outcome.[30] Additionally, clonal expansion of hMSC in culture is not efficient to produce sufficient numbers of hMSC needed for transplantation. As such, nonclonal expansion of a heterogeneous population of hMSC is more likely to be adopted in a clinical setting, despite variations in efficacy.

RENAL REGENERATION USING PLURIPOTENT STEM CELLS

PSC are at the forefront of regenerative medicine in kidney disease by virtue of their unlimited self-renewal and capacity to differentiate into all types of renal cells, which provides possibilities to overcome the current shortage of donor kidneys. The kidney consists of various types of cells, but its major progenitors are classified into three groups: nephron progenitor cells (NPC; SIX2+),[47] ureteric buds (GATA3+),[48] and interstitial stromal progenitor cells (FOXD1+).[49] Regarding kidney regeneration, Harari-Steinberg et al.[50] showed that engrafted human fetal NPC improve kidney function in a murine 5/6 nephrectomy kidney injury model.[50]

However, as the use of human fetus-derived NPC brings along ethical questions, PSC derived from reprogrammed somatic cells are likely to avoid any ethical issues.

There are a few reports that demonstrate the therapeutic effect of hiPSC-derived NPC. Toyohara et al.[51] reported that renal subcapsular transplantation of hiPSC-derived OSR1+SIX2+ renal progenitor cells (RPC) improves blood urea nitrogen and serum creatinine levels and ameliorates histopathological changes in a murine AKI model induced by ischaemia/reperfusion injury, whereas parenchymal injection of RPC did not show any therapeutic effects despite the cell engraftment.[51] As there was no evidence of integration of transplanted cells into the mouse kidneys, the observed therapeutic effect of renal subcapsular transplantation of RPC was anticipated to be due to renoprotective factors secreted by RPC, such as angiopoietin-1, vascular endothelial growth factor (VEGF), and hepatocyte growth factor. On the contrary, Imberti et al.[52] reported that hiPSC-derived RPC administrated via tail vein injection could engraft into damaged kidneys and restore renal function in mice with cisplatin-induced AKI.[52] Differences in engraftment efficiency between these studies might be influenced by the mechanism of AKI-induction, the route of administration of the RPC, and the quality of the transplanted RPC (depending on the differentiation induction method). The results of these studies suggest that the transplantation site plays a crucial role in the therapeutic effect, rather than progenitor cell engraftment. However, renal regeneration by secreted renoprotective factors relies on the kidney's intrinsic potential for structural repair or true regeneration, which is limited for the human kidney. To functionally restore or regenerate nephron structures within injured kidneys, engraftment of progenitor-like cells is indispensable.[50]

In the past decade, in-depth knowledge of mammalian kidney development has been translated into significant advances regarding directed differentiation of hiPSC into cells of the kidney lineage.[48,53-57] NPC derived from PSC possess the developmental potential of their *in vivo* counterparts and form renal vesicles under three-dimensional (3D) culture conditions, eventually self-organising into nephron structures. These so-called kidney organoids closely mimic the organisation of kidney epithelia, including structures expressing markers of podocytes, proximal tubules, loops of Henle, and distal tubules. Kidney organoids have been shown to facilitate the interrogation of renal toxicity, disease modelling, and mechanistic studies into human kidney development.[54,58-64] As such, it is hypothesised that nephron structures differentiated from these NPC might function *in vivo* as well. In fact, NPC have been reported to form functional glomeruli and tubular structures *in vivo*.[65-68] An overview of all studies exploring transplantation of NPC or NPC-derived tissues is provided in Table 1.

The study conducted by Sharmin et al.[65] described a novel transplantation method in which spacers were used to release the tension of host kidney capsules, which resulted in the differentiation of hiPSC-derived NPC into glomeruli.[65] Here, iPSC-derived nephron aggregates were cultured with mouse embryonic spinal cords to initiate tubulogenesis, after which cotransplantation of mixed aggregates of human umbilical vein endothelial cells and MSC allowed the formed glomeruli to connect with the blood vessels of the host and develop podocyte-specific features such as primary processes coupled with slit diaphragm-like structures. This suggests that not only targeted stem or progenitor cells, but also additional cell types need to be included to optimise efficient transplantation. On the other hand, Van den Berg et al.[66] succeeded in the formation of functional glomeruli and highly polarised renal tubules upon renal subcapsular transplantation of PSC-derived kidney organoids in mice.[66] Mouse endothelial cells were observed in glomerular structures within the transplanted organoids, indicating the construction of vascular networks. While both groups tried to enhance vascularisation by addition of VEGF, no additional effect of exogenous VEGF was observed. Together with gene expression data showing VEGF expression in podocytes, this might suggest that transplanted podocytes sufficiently provide endogenous attractants to support vasculogenesis in and around engrafted kidney tissues.

Another important factor for efficient regeneration using NPC concerns the timing of transplantation. Whereas Sharmin et al.[65]

transplanted NPC 1 day after spinal cord induction, Van den Berg et al.[66] transplanted kidney organoids formed by NPC after 18 days of CHIR99021 treatment. Furthermore, Bantounas et al.[68] reported that NPC differentiated for 12 days developed better nephron-like structures compared to NPC differentiated for 19 days when transplanted subcutaneously in mice.[68] Transplantation of NPC on Day 12 after induction of differentiation resulted in substantially more mature nephron structures compared to the structures formed in 3D organoids cultured *in vitro* for 12 weeks. Although no teratoma-like structures were observed in the clusters of engrafted NPC, grafts also contained cartilage and poorly differentiated kidney tissue. As the presence of heterologous cells may cause uncontrolled tissue formation, eventually leading to side effects during treatment, strict quality control of NPC prior to transplantation is of the utmost importance. Accordingly, a recent study of Phipson et al.[69] employed single-cell RNA sequencing to display the batch-to-batch variation in kidney organoid generation.[69] This underscores the importance of quality control measures and stable differentiation protocols before adopting kidney organoids for use in regenerative medicine.

Table 1: Overview of studies exploring *in vivo* transplantation of renal progenitor cell, nephron progenitor cell, or nephron progenitor cell-derived tissues.

Cell Type	Dose	Additive	Model	Species	Site	Findings	Reference
RPC Day 25-28	$1.5x10^6$ cells/ mouse	Ureteric buds cells-conditioned media supplemented with 50 ng/ mL BMP7, 0.5 mmol/L BIO, and 10 mmol/L Y-27632	Ischaemia/ reperfusion injury	NOD. CB17-Prkdcscid/J mice	Renal cortex	Improvement of BUN and serum creatinine levels	51
RPC Day 12	$0.5x10^5$ cells/ mouse	-	Cisplatin treated	NOD-SCID mice	Intravenous injection	Improvement of BUN and serum creatinine levels	52
NPC (Tagawa)	-	MSC, HUVEC, mouse embryonic spinal cord 5 ng/mL VEGF	Healthy	NOD/SCID/ JAK 3null mice	Caudal end of the kidneys	Nephron formation Vascularisation with host endothelial cells	65
Kidney organoids Day 7+18 (Takasato)	-	-	Healthy	NOD-SCID mice	Renal capsule	Nephron formation Vascularisation with host endothelial cells	66
NPC (Tagawa) derived from haemodialysis-patients	-	MSC, HUVEC, mouse embryonic spinal cord 5 ng/mL VEGF	Healthy	NOD/Shi-scid, IL-2γKO Jic mice	Caudal end of the kidneys	Nephron formation Vascularisation with host endothelial cells	67
NPC Day 12, 19 (Takasato)	1.0 or $3.0x10^6$ cells/ sites	Matrigel	Healthy	SCID-Beige mice	Subcutaneously into each of four dorsal sites	Nephron formation Vascularisation with host endothelial cells	68

BMP7: bone morphogenetic protein 7; BUN: blood urea nitrogen; HUVEC: human umbilical vein endothelial cells; MSC: mesenchymal stem cell; NOD: nonobese diabetic; NPC: nephron progenitor cell; RPC: renal progenitor cell; SCID: severe combined immunodeficiency; VEGF: vascular endothelial growth factor.

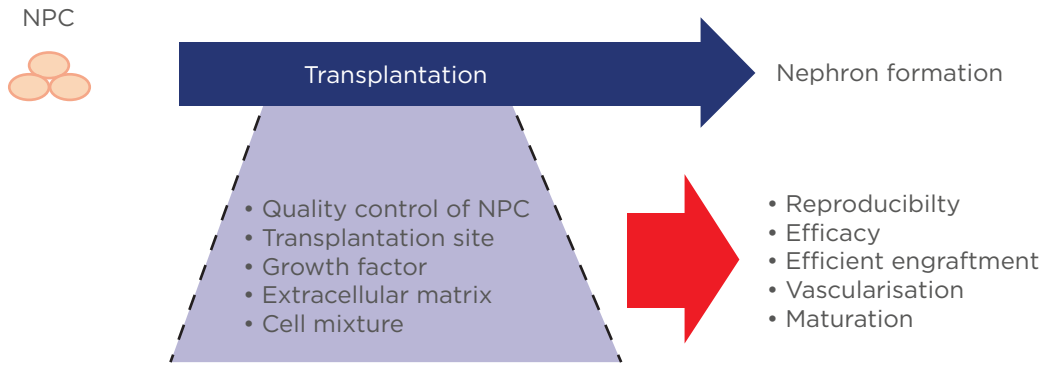

Figure 2: Future directions for optimisation of nephron progenitor cell-based transplantation to regenerate nephrogenic tissue.

NPC: nephron progenitor cell.

Recently, the Morizane group has developed a chemically defined protocol for differentiation of hiPSC into SIX2+ NPC with 90% efficiency. These NPC further possess the developmental potential to form organoids containing epithelial nephron-like structures expressing markers of podocytes, proximal tubules, loops of Henle, and distal tubules in an organised, continuous arrangement that resembles the nephron *in vivo*.[54,70] In this differentiation protocol, SIX2 immunostaining could be used as an intermediate quality control measure during organoid generation. However, depending on the protocol, more markers that could evaluate the differentiation status of hiPSC or induced NPC need to be established.

Although it has been argued that renal cells derived from PSC are immature, mostly reflecting first or second trimester equivalents, and therefore lack functional aspects of the native tissue, novel bioengineering methods have been explored to obtain more mature and functionally active kidney tissue.[71-73] The Lewis group reported an elegant method that combines bioprinting, 3D cell culture, and microfluidics to recreate the geometry and architectural complexity of kidney tubules.[71] The perfusable tubules within this model not only contained characteristic structural features, such as 3D convolution and open luminal architecture, but also expressed a variety of transporter proteins. More recently, the Morizane group adapted this method, in collaboration with the Lewis group, to enhance vascularisation and maturation of kidney organoids by applying fluidic shear stress during the later stages of the differentiation protocol.[74] The ability to induce vascularisation and morphological maturation of kidney organoids opens new avenues for therapies for renal regeneration.

However, a remaining challenge within renal regeneration comprises the formation of collecting ducts and connecting structures for drainage of urine. Taguchi et al.[56] developed a method to induce the ureteric bud from hiPSC, the precursor to the adult kidney collecting system which arises from the anterior intermediate mesoderm. Further co-culture experiments of ureteric bud and NPC in Matrigel (Corning Life Sciences and BD Biosciences) showed branching morphogenesis to some extent.[75] Despite the enormous potential of PSC-derived kidney cells and tissues for renal regeneration, further studies are required to optimise the conditions (e.g., timing, cell state, transplantation site) for efficient transplantation (Figure 2).

CROSS-SPECIES ORGAN GENERATION AND XENOTRANSPLANTATION

Although research on kidney organoids using PSC has dramatically advanced, the challenge of generating whole functional organs for transplantation remains. Blastocyst complementation is one such method in which a desired organ of human origin can be generated by integration of human PSC in animal

host embryos. In 1993, Chen et al.[76] restored lymphocyte development in Rag2-deficient mice (missing the inability to initiate V(D) J recombination needed for immunoglobin rearrangement) by injection of normal embryonic stem cells into the blastocysts of these mice.[76] The Nakauchi group created insulin-secreting rat PSC-derived pancreata in Pdx1-/- (pancreatogenesis-disabled) mice.[77]

Furthermore, the same group generated mouse PSC-derived pancreata in rats that could improve streptozotocin-induced diabetes by transplantation of the mouse–rat chimeric pancreata into mouse kidney subcapsules.[78] Transplanted pancreata normalised and controlled host blood glucose levels for >1 year in the absence of immunosuppressants (excluding 5 days of tacrolimus treatment after transplantation). Later, the Nakauchi group showed that the same approach can also be used in larger animals by generating exogenic pancreata from porcine PSC in apancreatic cloned pigs.[79] Recently, Wu et al.[80] reported that some types of hiPSC exhibit chimeric competency when introduced in post-implantation pig embryos.[80] Altogether, these studies reflect the therapeutic potential of interspecies blastocysts complementation for organ regeneration.

For the kidney, the same approach was extended to generate PSC-derived kidneys using Sall1-/- (nephrogenesis-disabled) mouse blastocysts.[81] However, nephrogenic tissues not under the influence of Sall1 expression, such as collecting ducts and microvasculature, were not complemented by the injected mouse PSC. Furthermore, whereas the authors were unable to obtain rat PSC-derived kidney in anephric Sall1-/- mice, conversely, mouse PSC-derived kidney tissue could be formed in the metanephric mesenchyme of Sall1 mutant rats.[82] Here, the newly-formed kidney tissue showed the expression of several key functional markers and proper ureter-bladder connections were formed, indicating the ability for urine excretion. Unfortunately, postnatal lethality of both Sall1-/- rats and mice complemented with mouse PSC-derived kidney tissue hinders any functional examination of the PSC-derived kidney tissue. As Sall1 expression is not limited to the kidney, but also found in brain, lung, and endocrine tissues, knockout of Sall1 might result in early-onset lethality. As a next step, disruption of alternative genes essential for kidney development should be examined.

Although blastocyst complementation holds great promise for regenerative medicine, the generation of human-animal chimeras might raise important ethical questions. This specifically applies to the use of human cells related to neural and germ lineages. Alternatively, methods ensuring that injected stem or progenitor-like cells solely develop as the desired target organ have been proposed. In these targeted organ complementation methods, precursor cells are transplanted into embryos lacking the specific target tissue. Using this method, Yamanaka et al.[83] specifically removed Six2+ NPC from mouse embryos followed by transplantation with rat NPC, resulting in the development of mature kidney tissue, including blood flow and connection with the mouse ureter.[83] Using the blastocyst complementation method with PSC, xenotransplantation of rat kidney tissue to mice could not be successfully established. This might suggest that the use of more differentiated progenitor cells (e.g., SIX2+ NPC) improves interspecies kidney complementation. While rodent chimaeras provide a platform for detailed investigation of factors that impact efficient xenotransplantation, larger host animals will be required to generate appropriately sized humanised organs. As sheep and pigs are considered as potential hosts for the development of humanised kidneys, major challenges remain regarding the evolutionary divergence between human donor cells and the host embryonic environment. As such, species differences in the embryologic development of the kidney and the corresponding nephrogenic niche first need to be clarified to facilitate efficient strategies for the generation of humanised kidneys.

CONCLUSION

This review described the progress of stem cell-based technologies with an emphasis on their potential for the regeneration of kidney tissue. Although hMSC are advisable as a cell source for stem-cell based therapies in terms of safety, adequate kidney regeneration is difficult upon hMSC treatment. Therefore, strategies using other stem cell sources need to be developed. The diversity of functions that the kidney

exerts in the human body relies on higher-order structures, including advanced tubular segments, microvasculature and a collecting system. In recent years, developmental studies have provided valuable insights in different stages of nephrogenesis along with the involved progenitor cells. Accordingly, several methods for differentiation of NPC and kidney organoids from PSC have been established, which thus far have enabled the formation of vascularised nephrons *in vivo.* Adoption of bioengineering platforms has shown to facilitate evaluation of NPC and kidney organoids in a controllable *in vitro* setting, allowing further clarification of the underlying developmental processes required for regeneration of functional kidney tissue. However, to produce human-sized kidney grafts, scale-up of stem-cell derived tissue might involve blastocysts or targeted organ complementation methods in larger animals. While most of these studies are currently performed in smaller animals, such as rodents, progress has been made at an astonishing rate. Altogether, these concerted efforts are opening the door towards a new generation of therapies for renal regeneration.

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Alteration of Glycaemic Balance due to Chronic Kidney Disease

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Abstract

The incidence of diabetes in patient populations requiring dialysis is constantly increasing. Metabolic disturbances in this group need focussed attention, particularly as carbohydrate balance is affected by specific disease-related factors. Beta-cell dysfunction, insulin resistance, and advanced glycation end-product accumulation are increasingly detected in the period preceding dialysis. Glycaemic control is also linked to the health of bone metabolism and control of renal failure-related anaemia. Novel opportunities in the assessment of glucose homeostasis, including continuous glucose monitoring systems, skin autofluorescence, and investigation of the metabolome, have resulted in significant developments in diagnostics and therapy. Regarding antidiabetic control, the major therapeutic goal for patients on haemodialysis (HD) is the alleviation of glycaemic fluctuation during the post-dialytic phase. The periodicity in antidiabetic regimes on HD and non-HD days is the preferable tool. For patients on peritoneal dialysis, the adverse impact of glucose originated from the standard solutions should be counterbalanced. This review focusses on the relationship between diabetes and HD or peritoneal dialysis and provides clinical suggestions to support the planning of individualised therapy. Nowadays, the number of patients with advanced renal failure is increasing. In current medical training, nephrological and diabetic education is separated within the internal curriculum. Thus, an average nephrologist is not trained in diabetic issues that would enable them to control the carbohydrate metabolism of a patient with renal insufficiency at different stages of glomerular filtration rate narrowing, and additionally is not permitted to change the choice of therapy. Conversely, a general diabetologist is not aware of the effects of kidney failure and dialysis on glycaemic control and is not familiar with the technological details of renal replacement therapies: special alterations related to nephrological factors are therefore not taken into account when treating diabetic patients with kidney disease. The article deals with the theoretical and practical issues of this clinical border area, helping the clinician to choose individual treatment for a particular patient. Guidelines for choice of oral and insulin therapy in this patient group, based on clinical experiences and theoretical considerations, are under continuous development, and definitive results are expected in the near future.

INTRODUCTION

Epidemiology of Diabetic Kidney Disease: Why is it so Important?

During recent years, a new classification of chronic kidney disease (CKD) was introduced in the literature because this condition can be grouped as diabetic renal (DKD) and non-diabetic renal disease (NDRD), respectively. This reflects the outstanding contribution of diabetes to the development and progression of kidney damage. The prevalence of diabetes among patients on dialysis is 40–50% in developed countries.[1] Challenges related to the control of carbohydrate homeostasis are more complex compared to those in diabetics without renal involvement. Indeed, even the definition of optimal glycaemic control in patients with varying degrees of renal failure is not fully clarified, and target values in individuals are significantly different.[2] During recent years, the appropriate management and assessment of carbohydrate homeostasis in patients with renal disease, as well as the impact of glycaemic control on morbidity and mortality, are at the centre of scientific interest. This increased awareness could improve healthcare providers' consciousness of and adherence to current guidelines. This review dicusses the relationship between diabetes and advanced stages of CKD, haemodialysis (HD), or peritoneal dialysis in detail.

Based on large trials performed in recent decades, good metabolic control hallmarked by HbA1c levels around 6–7% was shown to be protective against renal injury and other complications.[3] However, in the presence of moderate CKD, the factors influencing mortality and a further decrease in glomerular filtration rate (GFR) change markedly compared to those in the general population or in patients with early-phase renal failure. HbA1c, for example, is not clearly associated with further progression of CKD and mortality despite being the conventional glycaemic marker.[4]

Worldwide morbidity due to non-communicable diseases is in general improving; to the contrary, mortality related to CKD, and the prevalence of diabetic renal damage and associated disabilities, is increasing.[5] Based on prior studies (NHANES III, 10 years of follow-up; N=16,046) it is clear that mortality of patients with Type 2 diabetes mellitus (T2DM) is predominantly related to the development of renal complications.[6] The assessment of cardiovascular risk in patients with renal failure is increasingly emphasised. The risk is increased partly due to traditional factors (including inappropriate control of carbohydrate homeostasis), and partly due to non-traditional and dialysis-associated factors.

Uncertainties in the Diagnosis of Diabetic Kidney Disease

The evaluation of differences between patients with DKD and those with NDRD is challenged by two major facts. The phenomenon of burnt-out diabetes, a novel subtype of the disease, was described just 5 years ago (this condition occurs when impairment of renal function results in diminished elimination of endogenous insulin, but to a level that is still sufficient for appropriate blood glucose control: therefore, antidiabetic agents can be discontinued). The epidemiological classification of this patient group is not fully clear.[7] There are several factors that contribute to downward shifting of glucose homeostasis, including impaired renal and hepatic clearance of insulin, absence of gluconeogenesis in renal tissue, and, as a result of dialysis, improved insulin secretion and decreased uraemic toxicity. Patients with burnt-out diabetes should adhere to dietary recommendations. The re-initiation of any necessary antidiabetic therapies should be decided according to the results of continuous and rigorous blood glucose monitoring performed at home. Treating physicians should also perform the regular monitoring of micro and macro-angiopathic complications.

The contribution of diabetes to CKD is varied. Diabetes can be the cause of renal failure in up to one-third of cases; but it may also present as a comorbidity with CKD of other aetiologies. This presents a further challenge when the cause of renal failure is yet to be identified in patients on dialysis, and also when its impact on mortality and survival parameters is not clarified.[8] The prognostic value of specific diabetic conditions, including new-onset diabetes on dialysis and after transplantation, will be better characterised in the near future.

The Significance of Glycaemic Correction at the Time of Dialysis Initiation

The mortality of diabetic patients in the period around the initiation of dialysis is particularly high. Additional to standard risk factors (heart failure, high systolic and low diastolic blood pressure, acute renal failure) a GFR value of <45 mL/min/1.73 m^2 at the time of the referral to nephrologist is also a predicting factor.[9] This raises the notion that mortality associated with the initiation of dialysis can be improved if cut-off GFR values of referral are increased in diabetic conditions.[9] A patient with declining GFR requires meticulous attention to avoid life threatening hypoglycaemia and to prevent serious, acute cardiovascular consequences. Therefore, their medication regimen should be regularly re-assessed and adjusted according to carbohydrate intake and specific factors affecting renal health.

According to novel data, the quality of glycaemic control in the pre-dialysis phase determines the mortality after the initiation of dialysis. Analysing HbA1c and random blood glucose levels of 17,819 patients during a 1-year preceding dialysis revealed that the quality of carbohydrate homeostasis is associated with mortality during the first year of renal replacement therapy. Compared to patients with HbA1c levels of 6–7%, the mortality increased by a factor of 1.19 and 1.48 in patients with HbA1c levels of 8–9% and >9%, respectively. The occurrence of random blood glucose levels >11.1 mMol/L increased mortality by a factor of 1.34 compared to patients with glucose levels in the range of 5.5–7.0 mMol/L.[10]

Other observations indicate that strict glycaemic control in the early stage of diabetic nephropathy in patients with albuminuria >300 mg/day provided no benefit and did not prevent cardiovascular events.[11] A meta-analysis of 29,141 diabetic patients with no or mild nephropathy revealed that good glycaemic control (HbA1c: <7% and fasting blood glucose: <6.6 mMol/L) had no significant impact on risk of mortality, development of a condition requiring dialysis, or major cardiovascular events, and provided minimum benefit regarding the risk of myocardial infarction and progression of microalbuminuria.[12] The significance of the quality glycaemic control in earlier stages of DKD should be established by future studies. Previous results of large diabetological studies (UKPDS,[13] DCCT,[14] EDIC[15]) obtained one to two decades ago suggested that good glycaemic control correlated with better outcomes. Nowadays, however, the strength of this evidence is debated due to the change in the composition of global DKD population (with more elderly patients with comorbidities) and change in antidiabetic regimes. The long-term benefits of tight metabolic control on renal conditions are seemingly limited to those still not on dialysis.

MARKERS FOR QUALITY ASSESSMENT OF CARBOHYDRATE HOMEOSTASIS IN PATIENTS WITH RENAL FAILURE

Traditional Markers

Based on recent literature, the benefits of strict glycaemic control in the prevention of micro and macrovascular complications are not fully demonstrated. According to current guidelines, individualised targets should be established while considering the presence of co-morbidities, susceptibility to hypoglycaemic episodes, and predicted lifetime. This approach is of particular importance in patients with renal failure.

For the assessment of the quality of glycaemic control there are traditional and novel markers. Their role, clinical use, and justification are different in patients with renal failure compared to the general population. In older patients with renal impairment, hypoglycaemia may lead to catastrophic events including myocardial ischaemia, stroke, severe accidents, epileptiform attacks, or sudden death due to acute malignant arrhythmias.

According to some (but limited) data, variability in glucose levels may have a role in the development of DKD. One can assume that in the future, individual or professional continuous glucose monitoring (CGM) will be the standard tool for the recognition of hypoglycaemic events and the establishment of optimal therapy.[16] The self-check of glucose levels alone improved glycaemic control during a 3-month period, with an efficacy comparable to that of CGM. It is likely that the patients' increased awareness alone decreased the occurrence of hyperglycaemic

phases, while the frequency of hypoglycaemic events did not increase.[17] In addition, in a particular individual the estimated average of blood glucose levels based on HbA1C levels does not necessarily reflect real blood glucose levels: only CGM can provide reliable information on glycaemic control. Unfortunately, the wide use of CGM is financially limited.[18]

Another study demonstrated that high glycated albumin levels predict 4-year mortality in HD patients (N=1,255) better than HbA1c.[19] A meta-analysis (N=3,928 from 24 studies) also revealed a stronger correlation of average blood glucose levels with glycated albumin than with HbA1C levels, and that glycated albumin levels in patients with advanced renal failure predicted cardiovascular events more accurately than HbA1c.[20] Other investigators evaluated the relationship between the fasting blood glucose levels of patients with varying degrees of renal failure, and HbA1c, glycated albumin, and fructosamine levels. None of these markers were optimal for the assessment of glycaemic control in this population. Currently, however, HbA1c is still considered to be the traditional marker used for the assessment of the quality of glycaemic control; other non-traditional markers offer no benefits in prediction.

Novel Markers of Metabolism

Considering the phenomenon of metabolic memory, the lack of strong correlation between outcome and actual (short-term) glycaemic control in renal failure patients is not surprising. In general, diabetic nephropathy develops 10–15 years after the diagnosis of carbohydrate metabolic disorder, and the development of end-stage renal disease requiring dialysis lasts for several years after. However, the exact date of disease onset is not known at the time of T2DM diagnosis, and the quality of glycaemic control in a patient with advanced renal failure is not known in the long-term either; one cannot therefore establish the contribution of the quality of glycaemic control in preceding periods to the progression of renal impairment.[21]

Skin autofluorescence measurement is a tool that may better indicate the development of complications and risk of mortality compared to traditional markers of glycaemia. This parameter reflects the cumulative quality of glycaemic control during the preceding 5–10 years. The extent of damage to connective tissues is hallmarked clinically by osteoarthritic and musculoskeletal degenerative disorders and patient disability. [22]

Presumably, metabolic disorders will be assessed in a comprehensive way at the metabolome level, which reflects also the effects of diet and gut microbiome.[23] The notion of uraemic toxins is also under transition due to the recent results of metabolome research. Data suggest that diabetes has a more significant effect on some individual metabolite levels in the early phase of renal failure compared to the advanced phase.[24]

CHANGE OF CARBOHYDRATE METABOLISM WITH IMPAIRMENT OF GLOMERULAR FILTRATION RATE: THE IMPACT OF DIFFERENT FACTORS ON PROGRESSION

Lifestyle Factors and Diabetic Kidney Disease

Previous literature data clearly support that regular physical activity and adherence to dietary recommendations slow the onset and progression of long-term complications, including chronic renal failure. For corresponding details tailored to specific populations refer to national guidelines. The Mediterranean diet has an increasing role in the therapy of both diabetes and CKD.[25] In recent years, an association between T2DM and altered gut microbiome, characterised by the reduction of micro-organisms producing short chain fatty acids from carbohydrates, has been demonstrated.[26] The further alteration of microbiome during the development of nephropathy is less known. An association between oral cavity microbiome and CKD risk, as well as the blood level of certain cytokines (including IL-18), was also reported.[27] During the development of CKD, the gut microbiome is skewed and protein-metabolising bacteria become more abundant: locally produced uraemic toxins are absorbed and cause systemic toxicity, aggravating renal damage (and decreasing toxin elimination via the kidneys). Therefore, dietary interventions that have an impact on the gut microbiome may improve uraemic condition and slow CKD progression.[28]

A further challenge when treating this population is the patients' non-compliance and

non-co-operativeness due to deterioration of cognitive skills.[29]

Insulin Resistance in Chronic Kidney Disease

Because of altered insulin secretion and increased insulin resistance, CKD is associated with disturbed glucose homeostasis. Novel research data identified altered gut microbiome as the common cause of diabetic and uraemic, metabolic abnormalities.[30] All stages of CKD are hallmarked by insulin resistance. Several factors contributing to insulin resistance include decreased vitamin D levels, hyperparathyroidism, erythropoietin (EPO) deficiency, uraemic milieu and increased carbamylation of proteins due to high urea levels, inflammatory processes and increased oxidative stress, increased levels of cytokines, renin-angiotensin system activation, and acidosis. Standard factors of insulin resistance that are independent of renal function, including advanced age, obesity, dyslipidaemia, and hypertension, are also present. Hyperinsulinaemia via the MAPK pathway enhances vasoconstriction, cell proliferation, and cell migration, and results in alterations to the vascular wall, hence increasing the development of cardiovascular disorders.[31] A possible molecular mechanism of insulin resistance is the glycation of the insulin receptor and the impairment of cells' insulin binging capacity.[32]

Clinical observations support that CKD requiring dialysis is itself a risk factor of insulin resistance. Patients on a transplantation waiting list and treated with HD or peritoneal dialysis were compared to subjects from general populations who are at increased risk of T2DM. The group members were age, gender, and BMI-matched, with comparable glucose levels at baseline at the 120th minute of oral glucose tolerance test. Insulin production in the dialysed patients was significantly higher compared to that in the general population.[33]

The Kidney and the Carbohydrate Homeostasis

The role of the kidney in glucose homeostasis alters with the progression of renal function impairment. Under physiologic conditions, renal gluconeogenesis provides about 20–25% of glucose released into circulation: in the post-absorption phase, this figure increases up to 60%. In diabetic patients, the contribution of renal gluconeogenesis is increased further.[34] The increased risk of hypoglycaemia in CKD is partly due to the absence of renal gluconeogenesis.[34] Another factor contributing to increased risk associated with GFR impairment is the impaired renal elimination, as well as the more extensive or protracted effects of antidiabetic agents. Glomerular glucose filtration is also increased in diabetes. As a counterbalancing mechanism, tubular SGLT2 expression is increased, resulting in a later onset of glucosuria despite high glucose levels. With the development of renal failure, the extent of glucosuria decreases, while hyperfiltration caused by hyperglycaemia accelerates renal damage.[35]

Advanced Glycation End-Product Accumulation and Glycaemic Control

Both hyperglycaemia and CKD contribute to increased levels of glycation product. The increase of oxidative stress is associated with increased advanced glycation end-product (AGE) production. Renal proximal tubular cells degrade filtrated AGE products; therefore, elimination decreases as renal function impairment progresses. At the same time, AGE products accumulate in the mesangial matrix and contribute to renal damage in diabetic nephropathy.[36] In diabetic patients with GFR >30 mL/min/1.73 m^2 the skin autofluorescence values correlated inversely with the extent of renal impairment, and proportionally with early-stage atherosclerosis detected by ultrasound examination of carotid and femoral arteries.[37] The molecular basis of these phenomena is explained by the alteration of gene transcription induced by AGE-RAGE axis activation, resulting in the acceleration of inflammatory and oxidative processes and, finally, in endothelial cell dysfunction and arteriosclerotic plaque formation. AGE products induce permanent hyperglycaemia via biochemical alterations impairing glucose utilisation, and this provides a positive feedback for the increased production of further AGE molecules. Simultaneously, they play a role in the transition of smooth cells in vascular wall to bone-producing cells, which is considered as the first step of vascular wall calcification.[38]

Association Between Bone Remodelling and Carbohydrate Metabolism

AGE products exert multiple effects on pathological changes of bone architecture that finally result in osteoporosis. A major effect is the increase of osteoblast FGF23 production. A pilot study found an inverse correlation between intact parathyroid hormone and skin autofluorescence values.[39] Osteoblasts and adipocytes originate from a common, mesenchymal progenitor cell: during local remodelling processes there is a strong and bidirectional interaction between these two cell types. An anabolic effect of insulin is accelerated bone formation due to its binding to receptors on osteoblasts. Osteocalcin produced in bone tissue has an impact on insulin secretion and carbohydrate utilisation. Energy carrier molecules mobilised from fat stores support these processes, while the simultaneously mobilised cholecalciferol has an impact on calcium and phosphorous balance, as well as insulin secretion.[40]

Impact of the Correction of Anaemia on HbA1C Levels and Adverse Cardiovascular Outcomes

A study of 1,558 patients in CKD stage 3–4 revealed that HbA1C levels are only associated with mortality, risk of requiring dialysis, and cardiovascular events only in patients with haemoglobin levels >100 g/L: no correlation was observed in anaemic patients. HbA1C levels are influenced by a number of factors, including EPO therapy and conditions resulting in anaemia such as malnutrition or chronic inflammatory disorders.[41] HbA1C levels at the same glycaemic control are increased in the presence of iron deficiency,[42] while decreased upon EPO therapy.[43] Early observations from the Glycemic Indices in Dialysis Evaluation (GIDE) study indicate an inverse association between EPO therapy and HbA1C levels.[44] EPO therapy didn't show correlation with other alternative glycaemic markers, so lower HbA1C levels might be considered as a result of accelerated erythropoiesis, and therefore, this marker is not suitable for the characterisation of glycaemic quality.[43] EPO has pleiotropic, anti-apoptotic, and immune-modulatory activity. Presumably, it modulates glucose homeostasis through several means in addition to stimulated haematopoiesis.[45]

Beta Cell Dysfunction in Chronic Kidney Disease

Simultaneous to the impairment of renal function, uraemic toxin levels are also increasing: these toxins contribute to insulin resistance. In later stages, this process is accompanied by the dysfunction of beta-cells causing defective insulin secretion. Further factors accelerating beta-cell damage are acidosis, dyslipidaemia, hyperuricaemia, vitamin D deficiency, disturbed bone metabolism, and secondary hyperparathyroidism. However, results obtained so far are not unequivocal regarding the relationship between GFR impairment and the development of diabetes due to beta-cell dysfunction.[46] A large study (N=1,337,452; median duration of follow-up 4.9 years) demonstrated that, initially, a high urea level was an independent risk factor for the later development of diabetes.[47]

HAEMODIALYSIS AND GLYCAEMIC CONTROL

Common Features of the Two Dialysis Modalities

Depending on the glucose levels of the dialysis solution, the body loses or gains glucose during dialysis sessions. Both modalities have an impact on the metabolism of lipids, amino acids, and carbohydrates. Glucose entering from dialysis solution into the body potentiates insulin resistance and hyperinsulinaemia caused by the uraemic condition. The use of glucose-free solutions, on the other hand, is a risk factor of severe hypoglycaemic events in patients treated with antidiabetic agents. The permanent or intermittent parenteral glucose load has wide-ranging metabolic effects: for instance, via acceleration of oxidative stress, it contributes to increased glycation and has an adverse effect on cardiovascular outcomes.[48] Proinflammatory processes are also activated and accelerated at the time of the initiation of dialysis, depending on the extent of biocompatibility and pyrogen content of the dialysing agent. However, the increase of inflammatory marker levels is partly due to the failure of their renal elimination.

Data on the incidence of diabetes following the initiation of dialysis are still equivocal. A study from the Far East reported that during 13 years of

follow-up the risk of novel diabetes is decreased (HR: 0.49) in patients subjected to regular HD compared to controls (8,912 patients on HD, 2,092 patients on peritoneal dialysis, and 136 of controls). Of note, the decrease in risk was detected only in patients with HD; the incidence of diabetes in the peritoneal dialysis group was comparable to control patients, indicating that diabetes incidence was higher in patients treated on peritoneal dialysis than in those on HD (15.98 versus 8.69 case/1,000 patient years).[49]

Effects of Technical Parameters on Carbohydrate Metabolism in Haemodialysis

In HD patients, CGM revealed significant changes in carbohydrate metabolism depending on the day of dialysis session: average blood glucose levels and deviation of glucose levels were higher on days of dialysis than on those without sessions. This indicated a periodic change in insulin requirement.[50] In a 12-month study, the efficient removal of uraemic toxins with high-volume haemodiafiltration significantly improved malnutrition, the risk of protein malnutrition, and CRP values reflecting inflammatory processes.[51] AGE values and large molecular weight uraemic toxins are also removed from the body during dialysis sessions. In a small study, skin autofluorescence values decreased significantly (5.2%; p=0.02) 1 week after switching the patients to glucose-free dialysis solutions. Plasma autofluorescence values decreased after each HD session, probably due to the reduction of protein-bound fraction: the values reached their nadir after 2 weeks of therapy (p<0.05).[52]

Meals during HD increase the risk of hypotensive episodes due to redistribution of circulation accompanying digestion. This adversely modulates blood flow and impairs the efficacy of dialysis. However, even in the presence of glucose-containing dialysis solution (with a glucose level of 8.33 mMol/L) the metabolic state of diabetic patients is skewed into a state resembling that of fasting. During dialysis, the lactate, pyruvate, and alanine levels decreased, while 3-hydroxy-butirate and ketone body levels increased in diabetic patients. In addition, plasma insulin levels decreased due to filtration and adsorption during HD; diabetic patients with a deficient capacity to produce endogenous insulin were not able to compensate this phenomenon. Due to impaired glycolysis, this results in alternative mobilisation of energy sources, in imbalance of fat and protein metabolism into catabolic state, and increased gluconeogenesis. Similar alterations were not observed in HD patients without diabetes. Therefore, the administration of exogenous insulin at the end of the HD session should be individually considered and assessed.[53]

The Phenomenon of Glycaemic Disarray

The development of hypoglycaemic events in HD patients is the result of a complex array of factors that includes decreased appetite, failure of renal gluconeogenesis, impaired renal insulin clearance, glucose entering out of the body into the dialysing solution, the use of glucose-free dialysis solution, and increased erythrocyte glucose uptake during dialysis session. Therefore, the dosage of insulin and oral agents capable of inducing hypoglycaemia should be carefully determined, especially when both the efficacy and duration of these medicines increase. Several hours after HD, however, paradox rebound hyperglycaemia occurs, probably as a result of hormones counterbalancing insulin effects (similarly to that seen with Somogyi's effect). The insulin itself, along with peptide-type substances which impact on insulin secretion and effect, are removed during dialysis, while some membranes bind circulating insulin.[54] HD diabetic patients require individualised insulin dosing regimes for HD-days and non-HD days. The majority require less exogenous insulin during the post-dialytic period, while some require additional doses in the immediate post-HD hours. The modifications should be assessed according to blood glucose results in each patient.

Clinical Specificities in Haemodialysis

Lifestyle modification, including regular physical activity, is part of routine recommendations for HD patients. Some experts suggest controlled activity during dialysis sessions, while others prefer exercises on dialysis-free days that are recorded in a diary. In addition to the ageing of patients requiring dialysis, specific dietary considerations and cognitive impairment require individual adaptation of dietary modifications. Sarcopenia, (i.e., the severe decrease of active muscular mass) is increasingly frequent among

the dialysed patients: the prevalence of the so-called frailty condition may be up to 60%.[55]

Oxidative Markers in Haemodialysed Patients

An American study analysed a large number of patients (N=16,387) and reported a correlation between 2-year survival of HD patients and HbA1C levels. In patients with HbA1C levels >8.5%, the cardiovascular mortality was 18% higher compared to that in patients with HbA1c levels <6.5%. The increased mortality was due to a higher risk of myocardial infarction; stroke, peripheral vascular disease, and all-cause mortality were comparable in the two groups.[56]

The association between HbA1c levels and mortality is characterised by a U-shaped curve. The mortality was the lowest in patients with HbA1c 6–7% in the JDOPPS study; HbA1c <5% and 5–6% were 1.56 (95% CI: 1.05–2.33) and 1.26 (95% CI: 0.92–1.71), respectively.[57]

In T2DM patients on HD, both random plasma glucose levels and glycated albumin levels correlated with xanthine-oxidoreductase activity; therefore, this enzyme may be partially responsible for the acceleration of oxidative processes in poorly controlled diabetic patients.[58] In the general population the plasma xanthine-oxidoreductase activity correlated with BMI, smoking, uric acid and triglyceride levels, and insulin resistance index. The increased activity of the enzyme is accompanied by the generation of superoxide and other reactive free radicals. Therefore, this marker can be considered as the general biomarker of metabolic disorders.[59]

PERITONEAL DIALYSIS AND GLYCAEMIC CONTROL

Theoretical Considerations

Obligatory glucose absorption inherent with peritoneal dialysis increases cardiovascular risk. Daily glucose load ranges between 50–180 g depending on the regime used and transport characteristics. In diabetic patients, the blood glucose control should be intensified and individualised depending on hyperinsulinaemia and obesity. The benefits of peritoneal dialysis that are attributed to steady toxin and fluid removal, and maintenance of residual renal functions, begin to disappear if metabolic control is of not appropriate quality.[60] In peritoneal dialysing solutions containing high levels of glucose, so-called glucose degradation products (GDP) are formed during the sterilisation processes on high temperature. Characteristic GDP are methylglyoxal, acetaldehyde, formaldehyde, and 3-deoxyglucosone. These agents induce AGE production. Methylglyoxal also has a direct inhibitory effect on the insulin signalling pathway and increases insulin resistance. Actual guidelines on peritoneal dialysis, therefore, include the minimisation of glucose load during sessions and the use of glucose free solutions.[61]

Effects of Technical Parameters on Carbohydrate Metabolism in Peritoneal Dialysis

The systemic glucose exposure is increased by peritoneal dialysis. A study enrolled patients who are treated with peritoneal dialysis for at least half a year, but are not suffering in disorders of carbohydrate metabolism. Results indicated that in this peculiar population random plasma glucose levels correlated with daily intraperitoneal glucose exposure.[62] To avoid local and systemic damage caused by increased glucose load, glucose-free solutions and solutions with low GDP content are increasingly used, particularly when treating diabetics. Currently, there are no reliable data about the benefits of biocompatible dialysis solutions and icodextrin-containing, glucose-free polysaccharide solutions on technical survival and clinical outcomes.

Compared to patients using solely glucose-based solutions, patients who use icodextrin-based solution for long daytime dwell exhibited improved glycaemic control based on fasting glucose levels, daily cumulative insulin dose, and HbA1c.[63] In general, peritoneal dialysis regimes contain icodextrin solutions just once a day due to financial limitations and the fear of possible side effects (including allergic events, aseptic peritonitis, extensive ultrafiltration, and interference of absorbed maltose with some methods used for glucose measurements). However, patients who require strict glucose restriction and intensified ultrafiltration are increasingly treated with icodextrin twice a day or with a bimodal peritoneal solution containing both icodextrin and glucose.[64]

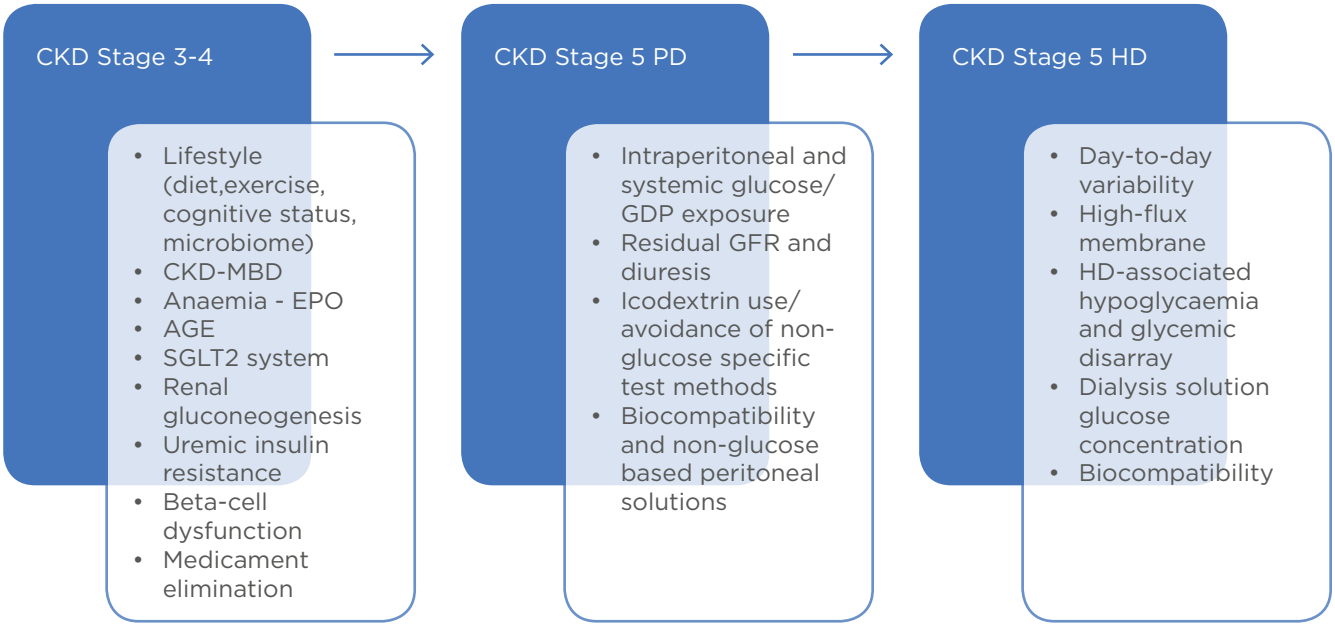

Figure 1: Main factors of glycaemic change in different states of renal failure.

AGE: advanced glycation end-product; CKD-MBD: chronic kidney disease-mineral and bone disorder; EPO: erythropoietin (therapy); GDP: glucose degradation products; GFR: glomerular filtration rate; HD: haemodialysis; PD: peritoneal dialysis; SGLT2: sodium-glucose co-transporter-2.

Clinical Specialities in Peritoneal Dialysis

The glycaemic control of diabetic patients with nephropathy depends in general on patients' adherence. Regular self-checks of glucose levels are of particular importance as therapy is based on actual blood glucose levels. Long-term glycaemic markers, however, provide less support to manage therapy, albeit patients with very low or those with very high blood glucose levels are at high risk of morbidity. In patients on long-term peritoneal dialysis, the gradual decrease of residual renal function and urinary output require the introduction of solutions with high glucose content in order to maintain optimal hydration. Although, in the short-term dwell time or the number of exchanges with the same low concentration glucose solution can be increased. This results in increased glucose exposure; therefore, the strategy of glycaemic control should be reassessed.[65]

Permanently high glucose exposure causes significant changes of peritoneal surface and leads its remodelling in a still unclarified way. Finally, the physiologic anti-adhesive properties are lost. Encapsulating peritoneal sclerosis is a rare, but dangerous complication of peritoneal dialysis; histologically it resembles diabetic micro-angiopathy. The most dominant risk factor is the length of period since the initiation of peritoneal dialysis supports the possible contribution of cumulated peritoneal glucose exposure. The episodes of peritonitis and the development of quick transporter character are further risk factors of encapsulating peritoneal sclerosis and indicate the pathogenic role of locally high glucose exposure.[66]

Epidemiological Data in Peritoneal Dialysis

In diabetes, the benefits of peritoneal dialysis compared to HD in terms of survival following the initiation of dialysis sessions were demonstrated only in those patients who reached optimal glycaemic control (HbA1c: <8%). If glycaemic control was not optimal, there was no difference in mortality between peritoneal and HD.[67] There are several unclarified issues, however, regarding the importance of optimal glycaemic control in dialysed patients. It is not known whether the impact of optimal glycaemic control on

prevention or delay of complications is so significant in nephropathy as in patients without renal failure. There is still no consensus even on optimal therapeutic targets either. The question of whether peritoneal dialysis should be the first-choice modality in diabetic patients can be answered after the extensive statistical analysis of large number of clinical data from patients initiating dialysis.[68]

CONCLUSIONS

Factors that are associated with CKD and related to the modality of dialysis (Figure 1) should be considered sufficiently when planning and controlling therapy of diabetic patients with renal failure. DKD raises several specific questions regarding the glycaemic control of affected patients. The optimal approach should be assessed individually in each patient, comprehensively considering the relevant technical parameters and clinical data. Targets may differ depending on whether the patient is in good general condition and waiting for transplantation, or if the patient is multi-morbid, disabled, and aged. In the first scenario, carbohydrate metabolism along with cardiovascular risk factors should be strictly controlled; in the second case, however, the major goal is the short-term improvement of overall life quality.

Carbohydrate metabolism of patients with advanced renal failure is more labile compared to that of the general diabetic population. It is affected by several additional factors related to renal failure itself and applied therapy, and subject to this review. Regarding antidiabetic control, the major therapeutic goals in patients on HD is the alleviation of glycaemic fluctuation during the postdialytic phase. The periodicity in antidiabetic regimes on HD and non-HD days is a preferable tool for individualised therapy. In patients on peritoneal dialysis, the adverse impact of glucose originated from standard peritoneal dialysis solutions should be counterbalanced.

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New Aspects of Fibrillary and Immunotactoid Glomerulonephritis

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Abstract

Renal diseases involving glomerular deposits of fibrillary material are an important diagnostic challenge for an ultrastructural pathologist. Several renal diseases are characterised by the presence of fibrillary material in the glomeruli. Two disorders of this type, termed 'fibrillary glomerulonephritis' (characterised by fibrils measuring approximately 20 nm in diameter) and 'immunotactoid glomerulonephritis' (characterised by larger, microtubular deposits), have been described. The possible relatedness of these two disorders and their potential association with other systemic illnesses are the subjects of current debate. Other multisystemic diseases, including amyloidosis and various forms of cryoglobulinaemia, can also present with fibrillary or microtubular deposits in the kidney.

The distinction between fibrillary glomerulonephritis, immunotactoid glomerulonephritis, and other processes that have similar ultrastructural features are discussed in this review. Recently, both in fibrillary glomerulonephritis and in immunotactoid glomerulonephritis, the presence of a DnaJ homolog subfamily member 9 has been detected. This antigen is not present in amyloidosis and could be involved in the pathogenesis of these diseases. This review will discuss the role and the relevance of this antigen.

INTRODUCTION

Glomerular deposits with fibrillary structure are encountered in several renal disorders. In some diseases, such as amyloidosis, fibril deposition is typically multisystemic and the biochemical nature of the fibrils is well understood. Additional groups of glomerulopathies involving noncongophilic fibrillary deposits have been described and are known as 'fibrillary glomerulonephritis' (FGN) and 'immunotactoid glomerulonephritis' (ITG).[1] Traditionally, the absence of congophilia has been used to differentiate FGN from amyloidosis. Recently, the discovery of the antigen DnaJ homolog subfamily member 9 (DNAJB9) has been detected in patients affected by FGN, regardless of their congophilia,[2] and DNAJB9 was the real marker of FGN and ITG more so than congophilia. This fact means that the congophilic properties of organised fibrillary deposits should not be solely relied upon in differentiating FGN from renal

amyloidosis. Mass spectrometry and DNAJB9 immunohistochemistry can be useful in making this distinction. Consequently, this study formulated a new distinction among the different types of FGN. Overall, evidence shows that congophobic FGN is significantly more prevalent in females, while the presence of a monoclonal protein on serum protein electrophoresis or immunofixation significantly prevails in the congophilic FGN.

FGN and ITG are uncommon renal diseases characterised by fibrillary amyloid-like glomerular deposits. FGN was first described in 1977 and is characterised by straight fibrils of 10–30 nm thickness with polyclonal Ig deposition.[3]

RESEARCH METHODOLOGY

Because the aim of this review was to find out what is new in the classification and differentiation between fibrillary and immunotactoid GN, the authors analysed the available papers on FGN and ITG, by a review of the currently available literature. A literature search was performed using PubMed (NCBI/NIH) with the search words "fibrillary glomerulonephritis" and "immunotactoid glomerulonephritis". As first-line research, the papers published in the last 3 years were examined. Papers were selected according to the relevance of the journal, the authors, the dimension of the study, and the novelty of the findings. In doing so, 20 recently published papers were selected, then the authors proceeded in a reverse chronological order and studies previously published were also included.

EPIDEMIOLOGY AND DISTINCTION BETWEEN FIBRILLARY GLOMERULONEPHRITIS AND IMMUNOTACTOID GLOMERULONEPHRITIS

FGN has been reported to account for 0.5–1.0% of glomerulonephritis, while ITG is 10-fold rarer[4] and was first reported in 1992.[5] Several authors suggest that fibrillary and microtubular Ig deposits should be considered as variants of the same glomerulopathy, referring the disease to a fibrillary immunotactoid GN.[6,7] Other authors highlight that it is essential to distinguish between ITG (microtubular) and FGN.[8,9] To date, most authors retain that FGN should be distinguished from ITG on immunopathologic, ultrastructural, and clinical grounds.[8,10-12] Table 1 reports the main immunologic and clinical characteristics that distinguish FGN and ITG.

Both diseases are most commonly idiopathic, but ITG, in particular, may be associated with monoclonal gammopathies[13] and chronic infections.[14,15] Haematological malignancies may be frequently found in patients affected by ITG.[10] In contrast to FGN, patients with ITG frequently have hypocomplementaemia and an underlying dysprotidaemia. The glomerular deposits are usually monoclonal.[16] The differential diagnosis of the two diseases may be easily performed using the algorithm shown in Figure 1.[17]

In a study by Fogo et al.,[18] limited by their institution, it was found that patients affected by FGN were significantly younger than patients with ITG. All patients were affected by marked proteinuria and microscopic haematuria, and 70% of patients with ITG had an associated haematopoietic disease with monoclonal proteins and abnormal plasma cell proliferation. ITG is characterised by glomerular deposition of larger microtubular structures (usually >30 nm in diameter) that have focal parallel alignment. In FGN, the microfibrils had a diameter of 14.0±0.5 nm, while the microtubular structures had a mean diameter of 42.3±0.3 nm.

More recently, Lusco et al.[19] and Fogo et al.[20] identified as characteristic of FGN the following key diagnostic features: 1) mesangial proliferation and variable endocapillary proliferation; 2) polyclonal IgG and complement component 3 (C3); and 3) randomly arranged fibrils in the mesangium and variably in the glomerular basement membrane (GBM), 12–22 nm in diameter and negative for Congo red stain. Similarly, key diagnostic features for ITG were: 1) mesangial proliferation and variable endocapillary proliferation; 2) often clonal Ig and light chain restriction; 3) microtubular in parallel array in the mesangium and variably in GBM, >30 nm in diameter.

The distinction between the two entities is not always easy because many diseases affecting the kidney may present similar structures in the kidney.

Table 1: Immunologic and clinical characteristics of fibrillary and immunotactoid glomerulopathies.

Characteristics	Amyloidosis (AL Type)	Fibrillary glomerulopathy	Immunotactoid glomerulopathy
Congo red staining	Yes	No (not always)	No (not always)
Composition	Fibrils	Fibrils	Microtubules
Fibril or microtubule size	8–15 nm	12–22 nm	>30 nm
Organisation in tissues	Random	Random	Parallel arrays
Immunoglobulin deposition	Monoclonal LC	Usually polyclonal (mostly IgG4)	Usually monoclonal
Glomerular lesions	Deposits spreading from mesangium	MPGN, CGN, MP	Atypical MN, MPGN
Renal presentation	Severe NS, absence of hypertension	NS with haematuria, RPGN	NS with haematuria and hypertension
Extrarenal manifestations	Systemic deposition disease	Pulmonary haemorrhage	Microtubular inclusions in leukaemic lymphocytes
Association with LPD	Yes (myeloma)	Uncommon	Common (CLL, NHL, MGUS)
Treatment	Melphalan + dexamethasone	Corticosteroid + cyclophosphamide	Treatment of the associated LPD

AL: amyloid light chain; CGN: crescentic glomerulonephritis; CLL: chronic lymphocytic leukaemia; GN: glomerulonephritis; LC: light chain; LPD: lymphoproliferative disorder; MGUS: monoclonal gammopathy of undetermined significance; MN: membranous nephropathy; MP: mesangial proliferation; MPGN: membranoproliferative glomerulonephritis; NHL: non-Hodgkin lymphoma; NS: nephritic syndrome; RPGN: rapidly progressive glomerulonephritis.

This point is well highlighted by a study reporting five cases of patients, in which fibrillary deposition presented in the kidney biopsies.[1] The authors stress that the comprehensive analysis of fibrillary glomerulopathies should include a perfect assessment of ultrastructural features (fibril diameter and substructure); exclusion of amyloidosis; correlation between light microscopy, histochemistry, and immunofluorescence; and a careful search for underlying conditions such as lymphoma, chronic disease, and cryoglobulinaemia.

FIBRILLARY GLOMERULONEPHRITIS

FGN was first reported in 1977[3] as a glomerulopathy with material very similar to amyloid that did not stain with Congo Red, although recently a variant has been identified that is Congo Red positive.[20] The term was later changed by Duffy et al.[21] who introduced the term 'fibrillary renal deposits and nephritis'. Finally, Alpers et al.[22] shortened the name to FGN.

FGN is characterised by the deposition of randomly arranged microfibrils with a diameter from 12 to 30 nm. At immunofluorescence, polyclonal IgG and C3 are present. In light microscopy, several histological patterns may be observed ranging from membranoproliferative GN, to mesangial proliferative GN, to diffuse proliferative GN, or membranous thickening of the capillary tuft.[23]

For the diagnosis of FGN, the use of electron microscopy is mandatory. Clinically, FGN manifests in proteinuria, often in the nephritic range. The disease course is generally progressive towards end stage renal disease. Fibrils recur in 50% of the transplanted kidneys but the recurrence is often benign.[24]

The pathogenesis of fibrillogenesis has not yet been elucidated. Fibril deposition is almost always limited to the kidneys, even if some reports describe extrarenal involvement.[25] According to other authors, these reports should be interpreted with caution.[26] In a series of reported FGN, fibrils co-localise with amyloid P.[27] In other series, fibronectin has been detected in the deposits,[28] but it appears that fibronectin is not an essential component of the fibrils.

All these findings allowed the improvement of the diagnostic algorithm shown in Figure 1, the updated version of which is shown in Figure 2.

In a recent study,[29] DNAJB9 was detected in patients affected by FGN. The proteome of these patients also contained IgG1 as the dominant Ig. In these patients, immunofluorescence and immunohistochemistry with an anti-DNAJB9 antibody showed a strong and specific staining of the glomeruli, similar to immune deposits. These findings confirmed a previous study[30] and identified DNAJB9 as a putative autoantigen in FGN. An immunoprecipitation-based multiple reaction that allows the measurement of serum levels of DNAJB9 has recently been developed. In patients affected by FGN, a 4-fold higher abundance of serum DNAJB9 was found and this suggested that serum levels of DNAJB9 could be a valuable marker to identify FGN.[31]

A different study[20] found that the proteomic signature of amyloid was not detected using mass spectrometry among cases of congophilic FGN. Additionally, DNAJB9 was not detected using mass spectrometry in all cases of FGN, regardless of congophilia, and was absent in cases of amyloidosis and in healthy individuals.

In conclusion, the distinction between FGN and amyloidosis should not be done only on congophilic properties, but by identifying the presence of DNAJB9 with mass spectrometry and immunohistochemistry.

The prognosis of FGN is generally poor, although remission may occur in a minority of patients without immunosuppressive therapy.[32]

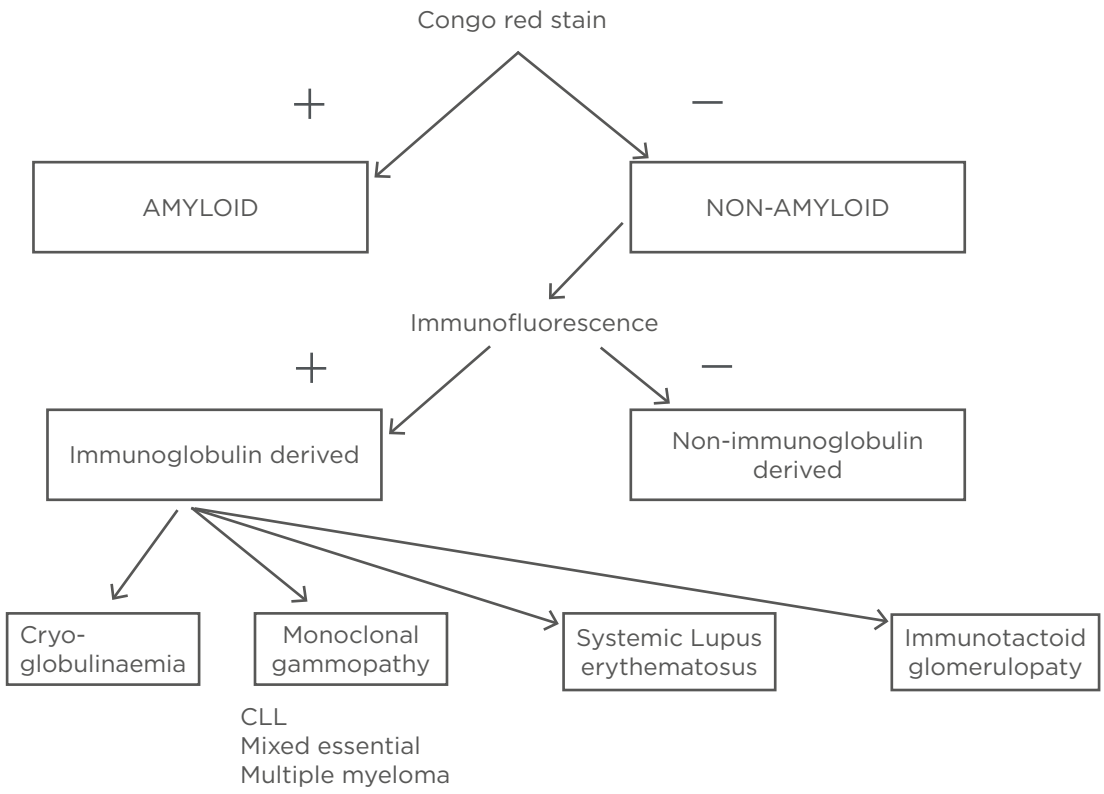

Figure 1: Algorithm for fibrillary glomerulopathy *in vitro* identification.

CLL: chronic lymphocytic leukaemia.

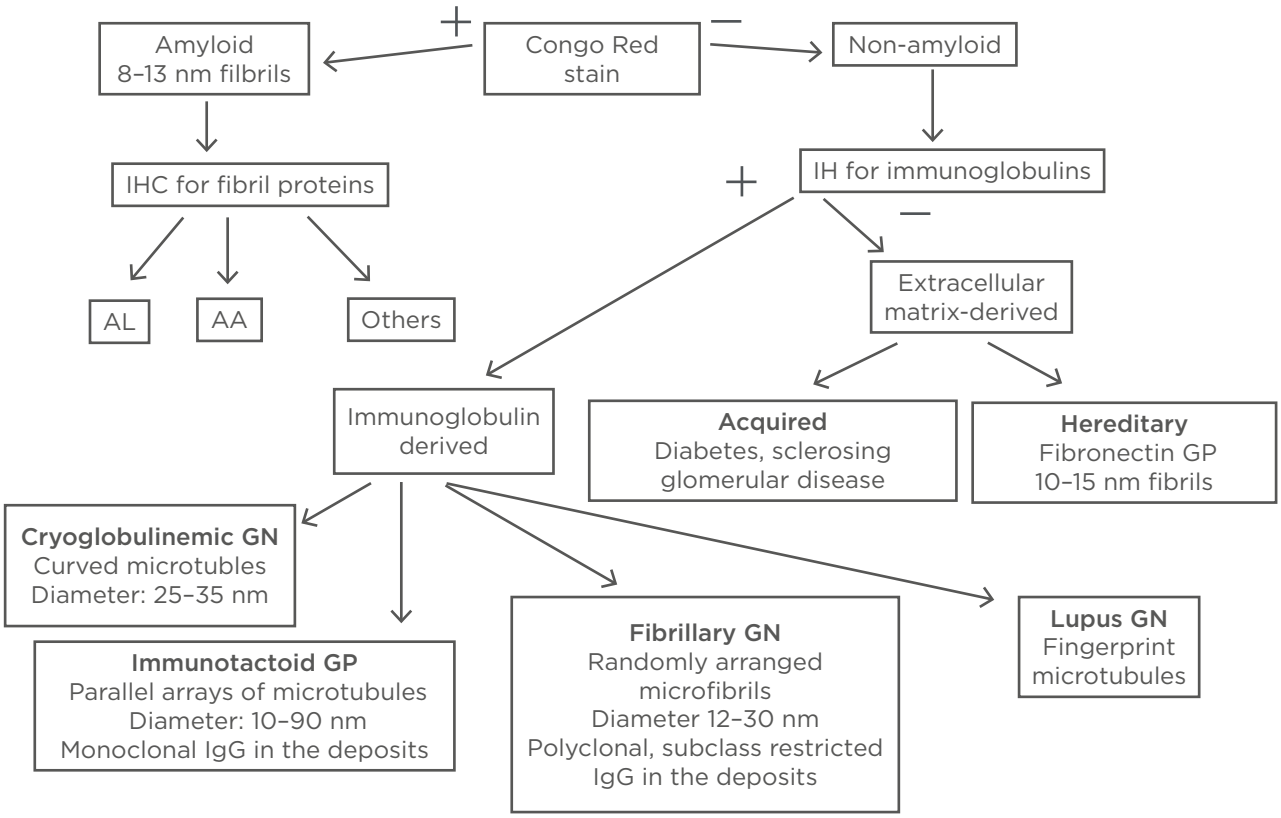

Figure 2: Glomerulopathy with organised deposits identification *in vitro*.

AA: amyloid associated protein; AL: amyloid light chain; GN: glomerulonephritis; GP: glomerulopathy; IHC: immunohistochemistry.

The published experience on the treatment of FGN includes several cases reports using the blockade of angiotensin II and a variety of immunosuppressive treatment including steroids and other immunosuppressants.[16]

However, no treatment has been shown to improve the long-term outcomes. In a recent study,[33] the use of rituximab was reported to treat 10 patients affected by FGN. The study documented the efficacy of rituximab, principally in patients with non-progressive renal failure. A recent study reported the efficacy of Acthar gel in the treatment of FGN.[34]

IMMUNOTACTOID GLOMERULONEPHRITIS

ITG was first used by Schwartz and Lewis[17] to describe a glomerular disease characterised by staining negative with Congo Red and having organised deposits that stain for IgG and complement. It is also defined by the glomerular deposition of microtubules that have distinct hollow centres, which can be 10–90 nm in size.[35] Because the deposition in ITG can appear similar to those in cryoglobulinaemia and lupus nephritis, these entities must be ruled out before a diagnosis of ITG can be made. Since the first descriptions, most published series included patients with underlying haematologic malignancies, excluding patients with systemic lupus erythematosus or cryoglobulinaemia.[10,11,18]

In the study by Rosenstock et al.,[4] the incidence of serum or urine monoclonal gammopathy was 67% in patients with ITG, versus 15% in those with FGN. Comparatively, patients with ITG have a significantly higher rate of paraproteinaemia than those with FGN (33% versus 7%, respectively).[7]

The disease is very rare and the pathogenetic mechanism of fibril deposition is not completely understood. The deposition should possess three features: 1) the Ig found in the deposits must be produced by lymphocytes and/or plasma

cells; 2) the Ig precursors must reach the kidney via the circulation; 3) the exclusive glomerular localisation of the deposits implies a role for local factors in fibrillogenesis.

Recent studies on CD2-associated proteins in knockout mice provide the support for a defect in glomerular function in ITG that could be responsible for tactoid formation and suggest that the effect is localised to the podocyte.[36,37]

Histologically the disease may present as a membranoproliferative GN, a diffuse proliferative GN, or a membranous glomerulopathy. The disease may recur after transplantation. The electron microscope shows microtubular, often parallel arrays with a diameter >30 nm.

The key diagnostic features of ITG are a mesangial proliferation with clonal IgG and light chain restriction on the already described microtubules. Ig is significantly more frequently associated with monoclonal protein and haematopoietic malignancy, most often B cell related. Patients present with nephritic proteinuria, reduced glomerular filtration rate, and hypocomplementaemia. The clinical improvement of proteinuria when treatment was directed at the haematopoietic disorder further support a role for monoclonal proteins in these patients.

Treatment with steroids alone or combined with cyclophosphamide, chlorambucil, or melphalan has been successfully used to induce complete or partial remission of the nephritic syndrome; fludarabine[4] or a combination of high-dose methylprednisolone and rituximab followed by alemtuzumab[38] has been shown to reduce proteinuria and improve renal function.

With a better understanding of the pathogenesis, clone-directed strategies, such as rituximab against CD20 expressing B cells and bortezomib against plasma cell clones, have recently been used in the treatment of this disease. These clone-directed therapies have been found to be more effective than immunosuppressive regimens used in non-monoclonal protein-related kidney diseases.[39]

CONCLUSION

The following key diagnostic and clinicopathologic features should be highlighted: the two diseases are distinct and not different aspects of the same disease as previously thought. In both diseases, mesangial proliferation and variable endocapillary proliferation are present. In FGN, randomly arranged fibrils in the mesangium and GBM are present, while in ITG microtubules in parallel arrays in mesangium and GBM are present: such microtubules are larger in diameter. In FGN, polyclonal IgG and C3 are present, while in ITG often clonal IgG and light chain restriction are present. The association with lymphoplasmacytic disorders is uncommon in FGN and common in ITG.

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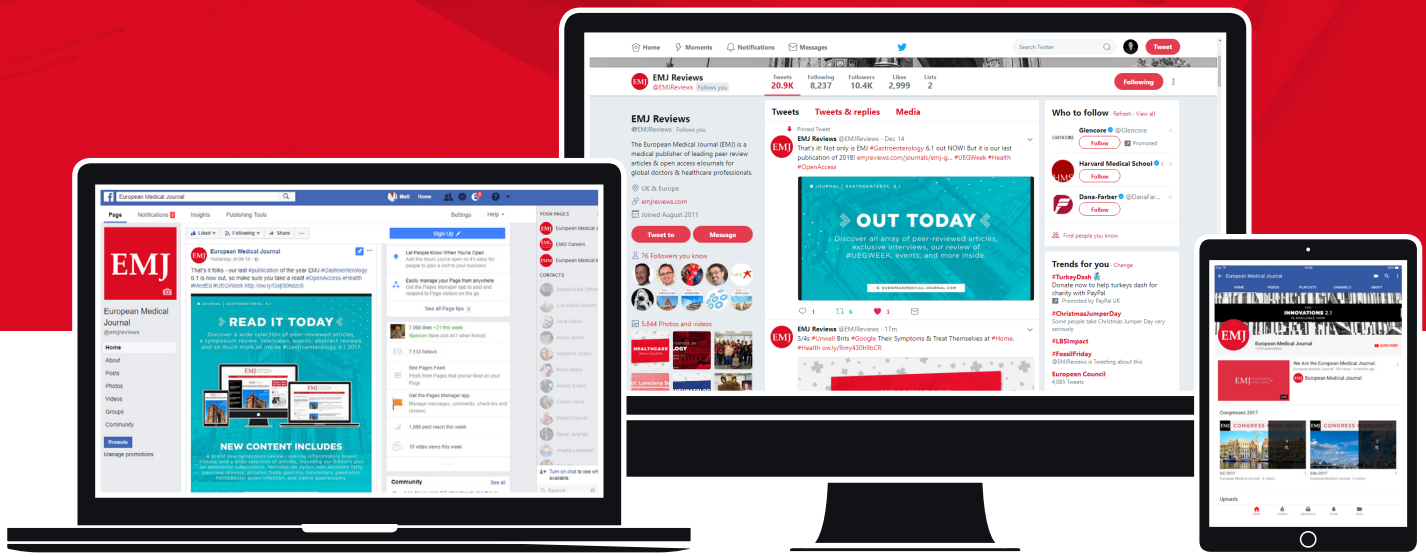

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Dengue-Associated Acute Kidney Infection: An Updated and Comprehensive Qualitative Review of Literature

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Abstract

Dengue is a viral infection transmitted by an *Aedes aegypti* mosquito bite that poses a major threat to public health worldwide. While acute kidney injury secondary to dengue infection is a potentially lethal complication, it remains one of the least studied complications of dengue fever. The underlying mechanism of dengue-associated acute kidney injury is complex because it involves multiple pathways that could independently lead to its occurrence. Therefore, the cornerstone of dengue-associated acute kidney injury management should involve prompt recognition and identification of the at-risk population and administration of appropriate supportive treatment in a timely manner with the aim of preventing both renal and non-renal morbidity and mortality.

INTRODUCTION

Dengue virus infection (DVI) is a vector-borne febrile illness which has a high prevalence in most tropical countries worldwide. DVI can be classified into dengue fever (DF), dengue haemorrhagic fever (DHF), dengue shock syndrome (DSS), and expanded dengue syndrome (EDS). The incidence of DVI has markedly increased throughout recent decades with reported worldwide cases increasing from 2.2 million in 2010 to 3.5 million in 2015.[1,2] DVI has the ability to cause a wide spectrum of clinical features from asymptomatic infection to severe systemic organ dysfunctions.[3,4] Renal involvements related to DVI have a variety of presentations, including proteinuria, glomerulonephritis, and severe acute kidney injury (AKI).[5] AKI is a significant, albeit poorly studied, complication of DVI.[6] The incidence of AKI in DVI has shown great discrepancy, with previous studies reporting a range from 0.83–14.40% with a mortality rate of 11.30–60.00%.[6-11]

Table 1: Mechanisms of acute kidney injury in dengue fever.

Mechanisms	Description
Viral action on renal tissue[13,14]	- Direct cytopathic effect of the viral antigen on renal tissues. - Immune mediated mechanism triggered by viral antigen with productions of antiviral antibodies. - Damage caused by inflammatory mediators released in response to the cytopathic effects.
Haemodynamic instability[12-19]	- Intense inflammatory response involves the release of inflammatory cytokines, activation of complement systems, endothelial injury which increases vascular permeability, and causes intravascular volume depletion. - Results in shock and reduction of renal perfusion with a consequent of acute tubular injury. - Most of the studies show higher frequency of hypotension and sepsis requiring inotropic support. - In contrast, literature also includes report of AKI cases without haemodynamic instability.
Rhabdomyolysis[20-24]	- Direct viral invasion mediated by myotoxic cytokines causes varied degrees of inflammatory infiltrates to areas of myonecrosis from histopathology. - Causes intrarenal vasoconstriction, renal tubular injury, or tubular obstruction. - Raised creatinine kinase levels with myoglobinuria in most cases with AKI. However, there are also reported cases with markedly raised creatinine kinase level without AKI.
Glomerulonephritis[25]	- Direct viral cytopathic effect causes variations in degrees of proteinuria which corelates with degree of thrombocytopenia. - Histopathology findings showed reversible mesangial proliferation with resolution of DVI.
Haemolytic uraemia syndrome[26]	- A triad of haemolytic anaemia, thrombocytopenia, and AKI. - Renal biopsy shows thrombotic microangiopathies with microthrombi at the arterials and glomeruli. - Most patients survived with recovery of renal function.

AKI: acute kidney injury; DVI: dengue virus infection.

PATHOPHYSIOLOGY OF DENGUE-ASSOCIATED ACUTE KIDNEY INJURY

Several mechanisms have been postulated for the pathogenesis of dengue-associated AKI (DAKI), including direct action by the virus, haemodynamic instability, rhabdomyolysis, haemolysis, and acute glomerular injury.[12] This is illustrated in Table 1.

DIAGNOSIS OF DENGUE-ASSOCIATED ACUTE KIDNEY INJURY

The authors found that most data currently available are derived from heterogenous case series and retrospective case studies. To further complicate the matter, EDS is a new clinical entity added to World Health Organization (WHO) guidelines to highlight the wide spectrum of atypical manifestations of dengue infection affecting various organ systems in DVI.[27]

The literature demonstrates a significant increase in DAKI, which can lead to a higher mortality rate and prolonged hospital stay.

Based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, AKI can be defined by either an increase in serum creatinine (SCr) by >0.3 mg/dL, an increase in SCr by >1.5-times baseline, or a reduction in urine volume <0.5 mL/kg/hour for 6 hours. It can be further

subdivided into Acute Kidney Injury Network (AKIN) stages based on change in SCr level. The Acute Dialysis Quality Initiative's (ADQI)[28] RIFLE criteria are also used in the classification of AKI. The acronym RIFLE defines three grades of increasing severity of acute renal failure (risk, injury, and failure) and two outcome variables (loss and end stage kidney disease).

The AKIN and RIFLE classifications were used to define AKI or DAKI in most documented case studies and retrospective case series, as was the conventional AKI criteria (SCr >2 mg/dL). A systematic review conducted by Mallhi et al.[27] found that the AKIN criteria was more sensitive as it picked up a higher incidence of DAKI (3.3–13.3%). Mallhi et al.[27] compared five studies which used the conventional definition (SCr >2 mg/dL) and AKIN criteria. They found that when using AKIN criteria, the incidence of AKI was higher. This can be explained because AKIN criteria classify AKI as a 1.5-times increase in SCr from baseline within 7 days (compared to conventional SCr >2 mg/dL), or as increased SCr >26.2 µMol/L from baseline within 48 hours.

In contrast, Kuo et al.[11] and Basu et al.[9] reported a very high incidence of DAKI when using RIFLE criteria (27.1% and 35.7%, respectively). The high incidence reported by Basu et al.[9] was because of the low number of dengue patients (28 patients) and the fact that the RIFLE criteria was only validated in half of the studied participants.

Table 2: Incidence of dengue-associated acute kidney injury in studies using various acute kidney injury classifications.

Study	Type of study	Number of patients	AKI definition	Incidence of AKI
Mehra et al.,[8] 2012	Retrospective	223	AKIN	10.80% AKIN 1: 5.4% AKIN 2: 3.1% AKIN 3: 2.2%
Khalil et al.,[7] 2012	Retrospective	532	AKIN	13.3% AKIN 1: 64.8% AKIN 2: 18.3% AKIN 3: 16.9%
Laoprasopwattana et al.,[10] 2010	Retrospective	75	SCr >2 mg/dL	3.9%
Lee et al.,[29] 2008	Retrospective	304	SCr >2 mg/dL	3.3%
Ong et al.,[30] 2007	Retrospective	7 (the study examined those who had died)	AKIN	14.2%
Sam et al.,[31] 2013	Retrospective	10 (the study examined those who had died)	AKIN	30.0%
Rigau-Oerez, Laufer,[32] 1995	Retrospective	23 (the study examined those who had died)	AKIN	17.4%
Rubina Naqvi,[33] 2016	Observational	3,525	RIFLE	1.2%
Mallhi et al.,[34] 2017	Retrospective	526	AKIN	AKIN 1: 29.6%
Haikal et al.,[35] 2017	Retrospective	266	AKIN	18.9%
Kuo MC et al.,[11] 2008	Retrospective	519	RIFLE	4.0%

AKI: acute kidney injury; AKIN: Acute Kidney Injury Network; DHF: dengue haemorrhagic fever; DVI: dengue virus infection; RIFLE: risk, injury, failure, loss, and end-stage kidney disease.

Most authors did not outline the reason why a specific classification was chosen. Nevertheless, many agreed that there is an urgent need to develop a consensus on the definition of AKI. This would help to demonstrate the true incidence and burden of disease, and it would also enable a comparison of studies in the field. Table 2 illustrates different studies that used AKIN, RIFLE, or conventional AKI criteria.

CLINICAL FEATURES OF DENGUE-ASSOCIATED ACUTE KIDNEY INJURY

A retrospective chart review by Naqvi et al.[33] demonstrated that the presence of fever, jaundice, oligo-anuria, and vomiting are strongly associated with development of DAKI. Based on a review of the literature, the authors did not find any validated specific constellation of symptoms at presentation of illness that may render a higher probability of developing AKI during the course of DVI.

However, in 2017, Mallhi et al.[34] proposed a predictive model consisting of different variables (including sex, type of DF, and transaminitis) which cause AKI in dengue patients based on a large retrospective cohort subjects of 667 dengue cases. By using this predictive model, the authors found excellent accuracy in predicting the possible development of AKI in dengue patients.[34]

MANAGEMENT OF DENGUE-ASSOCIATED ACUTE KIDNEY INJURY

General Management

Over the decades, there has been difficulty in understanding the exact mechanism of DAKI because of the complexity of its pathogenesis. Having a clearly defined approach to managing DAKI is important to prevent further complications that can cause an increase in morbidity and mortality rates. The main principle of management for DAKI is to restore the haemodynamic status with either crystalloid or colloids. Early detection of DAKI and prompt management of any subsequent complications is needed to reduce the chance of mortality as well as to prevent the development of chronic kidney disease (CKD) after recovery from the acute event. Clinical assessment of patients' haemodynamic and fluid status plays a major role in adequate volume replacement.[36]

Nevertheless, there is limited literature on the use of haemodialysis as a supportive treatment in DAKI while awaiting disease and renal recovery. There are currently no guidelines in terms of when to initiate renal support, the optimal dialysis dose, or the preferred modality of renal replacement therapy in treating AKI during DVI.[37] However, this should not become a barrier to initiating haemodialysis in the event of AKI, and most nephrologists or physicians will initiate dialysis based on conventional indications. One observational study investigated the use of haemodialysis as a supportive treatment in DAKI in Pakistan and studied 43 patients with DAKI who were administered fluids and haemodialysis.[33] A total of 37 patients had a complete recovery, and 6 died during the acute phase of illness. Of the 37 patients, 31 had received haemodialysis.[33]

Management According to Pathogenesis

Beside general management, DAKI patients should be managed as per the underlying AKI causes. Table 3 summarises the literature reported for the proposed mechanism of DAKI, management, and outcome of patients with DAKI.

Management of the Complications

Besides management of DAKI, there is a need to identify and treat the potential complications which almost invariably increase the rate of mortality or morbidity in patients. Complications that are associated with DVI are rhabdomyolysis, glomerulonephritis, hypotension, CKD progression, and prolonged hospital stay.

Rhabdomyolysis is a complication that is rarely taken seriously in DVI. It can increase the risk of AKI, which will eventually increase the patient's risk of mortality and morbidity. Patients with rhabdomyolysis usually present with dark-coloured urine or a non-specific type of generalised myalgia with correspondingly raised SCr kinase. Adequate fluid replacement and urine alkalinisation with sodium bicarbonate has been shown to improve the condition of rhabdomyolysis and improve the outcome of AKI.[43] Monitoring changes in creatinine kinase is necessary to guide management of the treatment

and assess response. There are three case reports, from 1996, 2007, and 2015, that showed good renal outcome for patients who had rhabdomyolysis with DAKI and had responded well to fluid replacement.[20,23,24]

Apart from acute tubular necrosis, the renal cortex, which is rich in glomeruli, can also be affected in DAKI. Patients with glomeruli involvement usually present with nephritic syndromes, which are proteinuria, haematuria, oedema, or hypertension. Immune complex deposition on the glomerulus has been proposed as one of the mechanisms of glomerular injury in DAKI.[13] There were a few case reports regarding renal biopsy proven glomerulonephritis as complications of DVI. Upadyaha et al.[17] reported a 15-year-old male with DAKI in whom renal biopsy showed IgA deposition. The patient was managed with fluid replacement and haemodialysis. There was evidence of resolution of the IgA deposition 6 weeks later, which was confirmed with repeated renal biopsy.

Table 3: Mechanisms of acute kidney injury in dengue fever.

Name of authors	Number of cases reported	Age, sex	Proposed mechanism of DAKI	Duration of stay	ICU	Renal biopsy	Management	Outcome	Cause of death
Dalugama, Gawarammana,[38] 2018	1	43, Female	No record	9	No record	No	Fluid, haemodialysis	Alive	N/A
Aishah Ali et al.,[39] 2015	1	64, Female	No record	14	No record	No	Fluid, haemodialysis	Died	Liver failure
Repizo et al.,[15] 2014	1	28, Male	Rhabdomyolysis induced acute tubular necrosis	21	No	Yes	Haemodialysis	Alive	N/A
Sargeant et al.,[36] 2013	1	25, Male	Rhabdomyolysis induced acute tubular necrosis	14	No	No	Fluid	Alive	N/A
Wijesinghe et al.,[40] 2013	1	42, male	Rhabdomyolysis induced acute tubular necrosis	9	No	No	Fluid, haemodialysis	Alive	N/A
Avasthi et al.,[41] 2012	1	30, male	Deposition of immune complex	35	Yes	No	Fluid, haemodialysis	Alive	N/A
Mehra et al.,[42] 2012	1	8, male	Acute tubular necrosis	No record	No	No	Fluid	Alive	N/A
Acharya et al.[21] 2010	1	40, male	Rhabdomyolysis induced acute tubular necrosis	No record	Yes	No	Fluid	Alive	N/A
Wersinga et al.,[16] 2006	1	48, male	Haemolytic uraemic syndrome	No record	No	No	Fluid, haemodialysis	Alive	N/A
Davis, Bourke,[22] 2004	2	33, male 33, male	Rhabdomyolysis induced acute tubular necrosis Rhabdomyolysis induced acute tubular necrosis	No record 2	No No	No No	Fluid Fluid	Alive Dead	 Multi organ failure

DAKI: dengue associated acute kidney injury; ICU: intensive care unit; N/A: not applicable.

Lizarraga et al.[25] also reported a 66-year-old woman who was admitted for DAKI and had IgG deposition along the glomerular capillary walls with antiglomerular basement membrane disease and myeloperoxidase positivity. The role of immunosuppressants and corticosteroids have been reported in 2012 and 2013, wherein renal biopsies of a 32-year-old female and 22-year-old female with DAKI triggered the presentation of lupus membranoproliferative glomerulonephritis.[44,45] Generally, glomerulonephritis triggered by dengue virus has a good outcome even though some cases require immunosuppressants. Hypotension or haemodynamic instability in which patients can enter a state of shock can be seen in DVI. During this period, there will be a release of inflammatory cytokines, activation of the complement system, endothelial injury, and plasma leakage which eventually results in loss of intravascular fluid. Haemodynamic instability and a state of shock can cause renal hypoperfusion which leads to AKI.[18]

One important, well-recognised complication of DAKI is the progression to CKD. A gradual decrease in glomerular filtration rate (GFR), as well as increased proteinuria, is the hallmark of the disease. Patients with AKI who required haemodialysis have a poorer outcome, including progression to end-stage renal disease.[47] To date, there is only one publication that studied the short-term renal outcome following AKI among dengue patients. In this study, 72 out of 526 patients diagnosed with dengue who developed AKI were recruited using AKIN criteria. Dengue patients who developed AKI were followed up for a post-discharge period of 3 months and renal recovery was assessed. A substantial number of patients at the end of the study had estimated GFR (eGFR) values that corresponded to the KDIGO classification of CKD. Of these, 50.7% (n=36/71) of patients had residual renal impairment compatible to CKD Stage 2, while 22.5% (n=16/71) of patients had eGFR corresponding to the advanced CKD stages, such as Stage 3 and Stage 4. Extended longitudinal follow-up of these patients may result in further improvement in eGFR.[48] This study highlighted the need to monitor the long-term renal function of patients who develop DAKI. Moreover, DAKI can cause prolonged hospital stays which can increase the rate of mortality and morbidity, as well as healthcare costs.

PREDICTORS OF DENGUE-ASSOCIATED ACUTE KIDNEY INJURY

Demographic

Male sex was found to be an independent predictor for developing DAKI,[7,27] with an odds ratio of 2:1.[34] In another retrospective study of 304 patients, DHF and being over the age of 30 were identified as risk factors for DAKI.[6] The incidence of AKI was higher in those above the age of 65 years.[29] An observational study that involved 43 patients with DAKI showed similar findings.[33] These findings were consistent in another cross-sectional study that recruited 217 DAKI patients.[50] The authors' review of the literature has found no specific racial predilection for DAKI. Similarly, socioeconomic status is not considered a risk factor for DAKI.

Severe Dengue with Hypotension

Severity of dengue infection, specifically DHF and DSS, was a significant predictor of development of DAKI and was associated with a higher mortality rate.[51] Similar findings were noted in a study involving paediatric population from Thailand.[10] Another study found that those with severe DF with hypotension shock requiring inotropic support had higher incidence of DAKI.[8,33] In addition, those requiring ventilatory support were at increased risk of developing DAKI.[49] Two recent studies have reported third-spacing and haemoconcentration as significant risk factors for DAKI. The incidence of DAKI risk was increased by as much as 4.7-fold in the presence of haemoconcentration or when the haematocrit level exceeded 46.5, indicating severe bleeding or third-spacing.[35,46] Notably, severe dengue with concurrent DAKI resulted in the worst outcome with the reported mortality rate as high as 64%.[6-8]

Pre-Existing Renal Disease and Autoimmune Disorder

Acute dengue infection with underlying renal parenchymal diseases predisposed the patient to develop DAKI. The associated renal diseases were glomerulonephritis, nephrotic range proteinuria, lupus nephritis, IgA nephropathy,

mesangioproliferative glomerulonephritis, and systemic lupus erythematosus.[6,27]

Comorbidities and Organ Involvement

A retrospective cohort study reported that co-existing viral hepatitis put DVI patients at risk of kidney failure. The study also emphasised the elevation of serum level of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) as additional risk factors for development of AKI.[8] Several other studies also reported that transaminitis was positively associated with the development of DAKI. The presence of multiple organ failure was also reported in the literature as a common predictor of DAKI where capillary leakage was a common feature.[8,27,34,51] Rhabdomyolysis with raised creatinine kinase levels could also lead to renal damage by infrarenal vasoconstriction, direct tubular injury, and tubular obstruction.[17,37] Other precipitating factors included concurrent sepsis or bacteraemia, low levels of albumin and bicarbonate, metabolic acidosis, prolonged activated partial thromboplastin time, thrombocytopenia, jaundice, gastrointestinal bleeding, elevated blood urea nitrogen, hyperglycaemia, and neurological involvement.[6-8,27,33,49] A higher baseline SCr in dengue patients was associated with higher risk of DAKI.[49] A small study that involved 75 patients showed that obesity with a weight standard deviation score of more than two was associated with an increased risk of DAKI.[10] Despite hyperglycaemia being a risk factor, diabetes was not associated with DAKI.[34,46] Length of hospital stay and intensive care unit admission were identified as independent risk factors for DAKI.[49]

Nephrotoxic drugs

The nephrotoxic drugs used in DVI were predominantly antibiotics, especially the potent antibiotics with systemic effect, such as vancomycin and carbapenems. Other drugs included amphotericin B and various antiviral medications. Additionally, a study in elderly dengue patients with comorbidities and multiple organ dysfunction found that the use of nephrotoxic drugs in dengue patients during hospitalisation had poorer renal outcomes.[34]

BIOMARKERS

The quest for AKI biomarkers is a field of intense contemporary research. Conventional biomarkers, such as urinary casts and fractional excretion of sodium, were non-specific in diagnosing the early stages of AKI. With the advent of functional genomics and proteomics, several studies have attempted to utilise molecular biomarkers in an attempt for early detection, risk stratification, and prognostication of DAKI. Several studies predicted an early phase of AKI based on differential expression of plasma and urine neutrophil gelatinase-associated lipocalin and cystatin C. This powerful biomarker acted as emerging independent predictors of AKI with an outstanding area under curve of 0.998 and 0.910 for 2-hour urine and plasma respectively, hence making it the most sensitive biomarker for AKI.[52] Other promising sequential biomarkers were IL-18, kidney injury molecule, liver-type fatty acid binding protein, and NF-κB. To date, none of these biomarkers have been tested in DAKI.[52]

DISCUSSION

The authors' review of the literature revealed wide variation of DAKI incidence, which was due to the difference in criteria selected to define AKI, namely the AKIN, RIFLES, and KDIGO classifications, and the heterogeneity of the studied population. There is no international consensus to date. Potential biomarkers like neutrophil gelatinase-associated lipocalin were being studied to diagnose AKI. There were no specific or standardised recommendations for medical treatment of patients with DAKI. Renal replacement therapy was still used conventionally as there were no updates on the techniques, timing to initiate dialysis, or dosing and modality in dengue patients. Fluid balance and replacement remained the main methods of treatment in addition to targeted therapy tailored specifically to the vast spectrum of dengue complications.

CONCLUSION

In summary, multiple retrospective studies and case series have demonstrated that DAKI is a frequent and highly significant complication of EDS. The morbidity and mortality rates are greatly increased when there is a delay in recognition

and consequent lack of prompt intervention. Hence, there should be an increased awareness among clinicians involved in the management of DVI. In addition, DAKI is associated with prolonged hospital stay and possible poorer renal outcome, thus indirectly adding to the healthcare burden. Presence of male sex, DHF, multiple organ dysfunction, rhabdomyolysis, diabetes, nephrotoxic drug use, and late hospitalisation may increase the incidence of DAKI. These findings clearly demonstrate the need for a high index of suspicion and vigilant monitoring in these groups of patients from the onset. The authors strongly believe a future prospective, multicentre study will likely aid clinicians regarding early predictors and clinicopathogenesis of DAKI, which will provide a better opportunity for timely intervention and a more positive outcome of the disease.

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Interventions for Preventing Infectious Complications in Haemodialysis Patients with Central Venous Catheters

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Abstract

Vascular access is the main risk factor for bacteraemia, hospitalisation, and mortality among haemodialysis (HD) patients. The type of vascular access most associated with bloodstream infection is central venous catheter (CVC). The incidence of catheter-related bacteraemia ranges between 0.50 and 6.18 episodes per 1,000 catheter days and increases linearly with the duration of catheter use. Given the high prevalence of CVC use and its direct association with catheter-related bacteraemia, which adversely impacts morbidity and mortality rates and costs among HD patients, several prevention measures aimed at reducing the rates of CVC-related infections have been proposed and implemented. As a result, many clinical trials, systematic reviews, and meta-analyses have been conducted to assess the effectiveness, clinical applicability, and long-term adverse effects of such measures. An integrative review was conducted on prophylactic measures against CVC-related infections in HD patients, identifying their potential advantages and limitations. A literature search was performed within multiple databases and meta-analyses on clinical experience with prophylactic antimicrobial therapy in HD CVC were reviewed and appraised.

INTRODUCTION

Haemodialysis (HD) is the most widely used dialysis modality worldwide and requires vascular access. Access options include arteriovenous fistula (AVF), arteriovenous grafts, and central venous catheter (CVC), which can either be tunnelled or not tunnelled.[1,2]

Infection is still the main cause of morbidity and mortality in patients treated with HD, despite advances in preventive care and antimicrobial therapy. According to the US Renal Data System (USRDS) registry, infection is the second cause of death in patients on dialysis. Among patients with chronic kidney disease (CKD) undergoing dialysis in the USA, the total death rate is 176 per 1,000 patient-years and septicaemia accounts for approximately 26 per 1,000 patient-years.[3-5]

Vascular access is a major risk factor for bacteraemia, hospitalisation, and mortality among HD patients. The type of vascular access most associated with bloodstream infection (BSI) is CVC (48–73%), which also increases

morbidity and mortality rates, as well as HD costs.[4-7] Others infections related to catheter usage are exit site infections (ESI) and tunnel infections.

The National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines discourage the use of catheters as vascular access for HD and recommend that <10% of patients should be using them for access.[7,8] However, the use of catheters for permanent HD access and, consequently, the number of prevalent HD patients dialysing through a CVC has progressively increased. According to the NKF, the number of prevalent patients dialysing through a catheter rose from 19% in 1998 to 27% in 2002.[7] Today, >80% of incident HD patients and 18% of prevalent patients use a CVC in the USA,[9,10] a reduction from 27% to 18% in prevalent patients.[11] Data from the Dialysis Outcomes and Practice Patterns Study demonstrates that 18% and 34% of prevalent patients use CVC in Europe and Canada, respectively.[8,12]

Catheter-related bacteraemia (CRB) is the most severe CVC-related infection. CRB is defined by the Centers for Disease Control and Prevention (CDC) as bacteraemia in a patient with an intravascular catheter, with at least one positive blood culture obtained from a peripheral vein, clinical manifestations of infection (i.e., fever, chills, and/or hypotension), and no other apparent source for the infection. This can be determined through either positive semiquantitative (>15 colony-forming unit/catheter segment) or quantitative (>103 colony-forming unit/catheter segment) culture, whereby the same organism is isolated from the catheter segment and a peripheral blood sample; simultaneous quantitative cultures of blood samples with a ratio of ≥5:1 (CVC versus peripheral) and a differential period of CVC culture versus peripheral blood culture positivity of >2 hours.[10]

However, in recent review articles, the standards requiring peripheral blood cultures have been questioned regarding the difficulties in performing venepuncture from HD patients, the fragility of vessels, peripheral vascular disease, and the priority of preserving veins for fistula creation.[10] Thus, simpler requirements, especially for epidemiological surveillance purposes, have been proposed to define CRB as positive blood cultures obtained from the catheter and blood line connected to the CVC, determining differential time to positivity.[11-13]

There are scarce data on epidemiology of ESI related to tunnelled CVC and most studies have focussed only on CRB.[17] ESI in tunnelled CVC rate ranged from 0.35 to 8.30 episodes per 1,000 catheter days.[14-17] According to Goulart et al.,[14] the overall incidence of ESI was 3.50 per 1,000 catheter days. Risk factors for ESI were presence of diabetes and tunnelled CVC implanted in femoral site (relative risk [RR]: 1.56, 95% confidence interval [CI]: 1.35–1.89, and RR: 1.62, 95% CI: 1.22-1.94, respectively; both p<0.05). The most frequent agents of ESI were Gram-negative (69%), mainly *Serratia marcescens*, *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* extended-spectrum β-lactamase (ESBL)-producing. Across the time period, there was a change in aetiologic agents; *Pseudomonas* and ESBL agents became more frequent, while *Proteus* and *E. coli* became less frequent (p<0.05). Among Gram-positive agents, 59% were resistant to methicillin. On the other hand, Gram-negative bacilli were not often multidrug-resistant. The catheter was removed in 17% of patients due to unsuccessful treatment of ESI and was associated with *Pseudomonas* (p=0.04) and BSI caused by the same agent of ESI (p=0.03). Catheter survival was shorter in the ESI group (logrank: 2.92; p<0.001). These data suggest the routine application of topical antibiotic ointments to prevent ESI related to CVC caused by Gram-negative agents.[17]

CRB rate is highest in HD patients using a CVC and increases linearly with the duration of catheter use. The incidence of CRB ranges between 0.5–6.1 episodes per 1,000 catheter days.[10,18] Several multicentre randomised studies have shown that the rate of catheter-related CRB is much higher than that of AVF-related BSI. CRB can lead to bacterial endocarditis, epidural abscess, septic arthritis, and septic embolism.[4]

CVC entails a risk of developing sepsis 2–5-fold higher than AVF and is therefore associated with a 25% increase in cost.[10] CVC use is associated with an independent increase in mortality rate.[12] Rates of mortality from infection within the first year of HD are currently 2.4-times greater than in 1981, a fact widely attributed to the use of CVC.[10]

In addition to the potential complications inherent to infectious processes, the rate of adverse cardiovascular events increases (up to 2-fold) after an episode of sepsis. As a result, morbidity, hospitalisation rates, and treatment costs increase, while survival rates decrease.[5,10]

Within the 24 hours after insertion, micro-organisms often form a biofilm in 100% of the catheters.[13] Many microorganisms may adhere to the CVC surface or become incorporated within a fibrin sheath that envelopes the CVC. The adherence of organisms to the catheter surface initiates biofilm production. Biofilm is a community of organisms protected by an exopolysaccharide matrix that is stimulated and secreted by the organisms. Mature biofilms develop high resistance to systemic antibiotics requiring high concentrations for bacteria elimination.[10,13,19-21]

There are two main routes by which organisms enter the bloodstream to cause CRB: an extraluminal pathway and an intraluminal pathway. The extraluminal pathway involves initial contact between skin surface organisms and the external surface of the catheter at the time of CVC insertion, or before complete exit site healing and subcutaneous tunnel endothelialisation. The intraluminal pathway involves transfer of organisms by contact from the hands or skin accessing CVC tips.[9,19,21]

Given the high prevalence of CVC use and its direct association with CRB, which adversely impacts morbidity and mortality rates among HD patients, several prevention measures aimed at reducing the rates of CVC-related infection have been proposed and implemented.[19] As a result, a large number of clinical trials, systematic reviews, and meta-analyses have been conducted to assess the effectiveness, clinical applicability, and long-term adverse effects of such measures.

This article aims to review prophylactic measures against CVC-related infections in HD patients, identifying their potential advantages and limitations. A comprehensive search was performed within Google Scholar, PubMed, and Science Direct databases from January 2008 to January 2018, using the following search terms: "hemodialysis", "tunnelled central catheter", "catheter-related bacteraemia", and "prophylactic antibiotic therapy".

PROPHYLACTIC NON-ANTIMICROBIAL MEASURES AGAINST CENTRAL VENOUS CATHETER-RELATED INFECTIONS IN HAEMODIALYSIS

The training and education of healthcare personnel in manipulating catheters regarding universal hygiene precautions has been noted as the key step toward infection prevention.[14] The introduction of a catheter care protocol, which followed the guidelines published in 2002 from the CDC, resulted in a decrease in CRB incidence from 6.7 to 1.6 episodes per 1,000 catheter days.[16] Top general precautions include washing hands with conventional soap and water or with alcohol-based hand rubs before and after palpating catheter insertion sites, and before dressing a CVC.[19,21]

The use of a sterile gown, sterile gloves, and sterile full-body drape during CVC insertion is defined as a maximum sterile barrier (MSB). In a randomised controlled trial, maximal sterile barrier precautions were compared with sterile gloves and a small drape during the placement of CVC. The MSB group had fewer episodes of both catheter colonisation and BSI (RR: 0.32; 95% CI: 0.10–0.96; p=0.04 and RR: 0.16; 95% CI: 0.02–1.30; p=0.06, respectively).[19]

Other measures include selection of the solutions used for exit site cleaning, dressing material, catheter antimicrobial impregnation, catheter material, topical ointments, and intraluminal compounds known as lock therapy.[14,16]

Superior skin and exit site cleaning have been demonstrated using chlorhexidine >0.5%. However, 70% alcohol or 10% povidone-iodine remain effective alternatives if chlorhexidine cannot be used.[10,19]

A meta-analysis of 4,143 catheters (1,493 CVC, 53 of which were used for HD), suggested that chlorhexidine gluconate reduced the risk for CRB by 49% (95% CI: 0.28–0.88) when compared with povidone–iodine. The absolute risk reduction was 7.1% for colonisation and 1.1% for BSI. The test for heterogeneity of treatment effect was significant for catheter colonisation (p<0.001), but not for CRB (p=0.200).[17] Available evidence indicates that the use of chlorhexidine would result in a 1.60% decrease in the incidence of CRB, a 0.23% decrease in the incidence of death,

and a saving of $113 per catheter.[14] Recent data indicate no significant differences between transparent, semipermeable dressings and standard gauze dressings regarding CVC-related infections in HD patients. The CDC recommends the use of a chlorhexidine-impregnated sponge dressing for temporary, short-term catheters in patients >2 months of age, if CRB rate is not decreasing despite proper personnel education and training.[19] Specific recommendations regarding the use of tunnelled catheters and the infection preventive measures that should be taken during their use remain unavailable and surrounded by controversy.[16]

The material the catheter is made from influences microbial adherence and the ability to form biofilm. Polytetrafluoroethylene or polyurethane catheters have been associated with fewer infectious complications.[19] Most dialysis catheters are made of silicone or polyurethane. However, whether these materials differ in their susceptibility to biofilm formation after catheter placement has not been investigated.[21]

The use of catheters coated with antimicrobial agents in intensive care units is associated with reduced catheter colonisation and decreased catheter-related BSI incidence, and would therefore be a useful option for HD in patients at high risk for CRB.[21-24] However, the few studies addressing the impregnation of tunnelled catheters for HD as a prophylactic measure against infections have shown conflicting results.[21]

MAIN STUDIES USING PROPHYLACTIC ANTIMICROBIAL IN HAEMODIALYSIS CENTRAL VENOUS CATHETERS

Topical Antibiotics

The application of topical antibiotic ointments at the CVC exit site has been shown to be associated with a 75–93% reduction in the risk of CRB. However, some agents are incompatible with some catheters, making it necessary to check manufacturers' recommendations before applying any agents on catheters.

Mupirocin, povidone–iodine, polysporin triple antibiotic ointment (gramicidin + bacitracin + polymyxin B), and medical honey have been the most commonly studied substances.[10] In 2002, Johnson et al.[20] conducted a randomised trial comparing the effect of exit site application of mupirocin versus no ointment in 50 HD patients with tunnelled catheters. Mupirocin reduced the incidence of exit site infection (6.6 episodes per 1,000 catheters days versus 0 in the mupirocin group; p<0.050) and CRB (35% versus 7% in the mupirocin group; p<0.010), and also increased median bacteraemia-free survival from 55–108 days (logrank score: 7.0; p<0.010). This improved infection-free survival was explained by a reduction in *staphylococcal* infection log-rank: 10.7; p=0.001).[25]

James et al.,[26] in a meta-analysis involving 15 studies with HD patients, evaluated the efficacy of topical antibiotic use or lock therapy compared to non-use of antibiotics for reduction of CRB and ESI related to the catheter. Both prophylactic antibiotic therapies reduced BSI rates and catheter withdrawal compared to non-use of prophylactic antibiotics. The antibiotic in the exit site also reduced ESI rates (0.06 versus 0.41 infection per 100 catheter days) and this reduction was not observed in studies containing lock therapy. However, in the studies analysed, several types of antibiotics and other associated interventions were used, making it difficult to analyse the individual impact of the topical antibiotic, in addition to a short follow-up period.

In 2010, Cochrane published a review on interventions to prevent CRB in HD patients. The analysis included 10 studies, totalling 786 patients; the studies evaluated interventions with topical use of mupirocin, triple polysporin, povidone-iodine, or medicinal honey, versus placebo, another antiseptic, or no topical antibiotic. They found that the use of ointment with mupirocin reduced the risk of ESI caused by *S. aureus* (RR: 0.18, 95% CI: 0.06–0.60; p<0.05) and CRB (RR: 0.17; 95% CI: 0.07–0.43; p<0.05) and triple polysporin ointment reduced the risk of CRB (RR: 0.4, 95% CI: 0.19–0.86; p<0.05) and all-cause mortality (RR: 0.22, 95% CI: 0.07–0.74; p<0.05), but with no effect on mortality related to infection. Povidone–iodine ointment reduced the risk of CRB (RR: 0.10; 95% CI: 0.01–0.72; p<0.05) and the use of topical honey did not significantly reduce either the risk of ESI or the risk of bacteraemia associated with a catheter when compared to mupirocin or povidone-iodine ointment.[27]

Since 2011, the CDC has recommended the use of ointment in the ES of the catheter after insertion and in each HD session. The use of povidone–iodine ointment or the one containing bacitracin, gramicidin, or polymyxin B is recommended, but the latter is no longer available in the USA and has never been available in Brazil. The use of ointment containing bacitracin, neomycin, or polymyxin B is cited as an option, but there are a lack of studies demonstrating efficacy in the prevention of ESI and CRB. Other options would be mupirocin or for the dressing to be impregnated with chlorhexidine. However, the CDC emphasises the risk of developing bacterial resistance, the possibility of the ointment being ineffective against the pathogens responsible for the infections, and the possible chemical interaction between the ointment ingredients and the catheter material.[28,29] The 2006 Guideline of the Canadian Nephrology Society recommends the use of topical antibiotics as a form of prophylaxis.[14] However, despite mentioning the use of antibiotics and the use of medicinal honey in the ES as a preventative measure of CRB associated with the catheter, since there are no studies that evaluate the development of bacterial resistance in the long term, the KDOQI guideline does not include this practice in its recommendations.[4]

Thus, routine use of topical antibiotics in the exit site of CVC is not widely used and should be based on the rates of local infections and the practice of each centre.[30]

Antimicrobial Lock Solutions

Although some studies between 2006 and 2010 have assessed the efficacy of antimicrobial lock solutions (ALS) in preventing BSI, most of them had significant limitations: these included the use of a small number of patients; many studies being retrospective, while others, despite being prospective, had short follow-up periods; some included patients with short-term and long-term catheters; and some used several solutions concomitantly, with or without antibiotics.[31-33]

The authors evaluated the efficacy of catheter-restricted filling using antibiotic lock solution in preventing CRB.[34] A total of 233 HD patients requiring 325 new tunnelled catheters were enrolled in this study. Patients with a tunnelled catheter were assigned to receive either antibiotic–heparin lock solution (antibiotic group: cefazolin 10 mg/mL, gentamicin 5 mg/mL, and heparin 1,000 U/mL) or a heparin lock solution (no-antibiotic group: heparin 1,000 U/mL). CRB developed in 32.4% of patients in the no-antibiotic group and in 13.1% of patients in the antibiotic group. CRB rates per 1,000 catheter days were 0.57 in the antibiotic group versus 1.74 in the no-antibiotic group ($p<0.0001$). Kaplan–Meier analysis also showed that mean CRB-free catheter survival was significantly higher in the antibiotic group than in the no-antibiotic group log-rank: 17.62; $p<0.0001$). There was no statistically significant difference between the two groups in drug-resistant germs. There were statistically significant differences between the two groups in the catheter removal causes, with higher rate of infectious cause in control group (12.32 versus 2.22%; $p<0.0001$) and mechanical cause in ALS group (28.26 versus 37.78%; $p<0.0001$). The results suggest that cefazolin and gentamicin, used as antibiotic lock solution, may be beneficial in reducing the CRB rate in HD patients with a tunnelled catheter, without association with the emergence of resistant strains. However, mechanical complications were more prevalent in the antibiotic group.

Labriola et al.[35] published a meta-analysis in 2007 that included eight randomised studies (829 patients, 882 catheters, and 90,191 catheter days) comparing ALS to a standard heparin lock in CRB prevention. While four of the studies included tunnelled catheters, only one included exclusively non-tunnelled catheters, and three studies included both tunnelled and non-tunnelled catheters. ALS significantly reduced the risk of CRB (risk ratio: 0.32; 95% CI: 0.10–0.42; $p<0.05$). The authors concluded that the significant reduction in the incidence of CRB achieved in the ALS groups was similar to published reports from units with low bacteraemia incidence and, presumably, stricter hygienic measures. Furthermore, the limited follow up of the studies included in this meta-analysis did not allow for the assessment of the onset of adverse events or bacterial resistance with longer use of lock therapy.

In 2008, Jaffer et al.[36] performed a meta-analysis of seven studies including a total of 624 patients and 819 catheters (448 tunnelled, 371 non-tunnelled) to determine the efficacy of ALS in reducing CRB in HD patients. Catheter-related

infection was 7.72-fold less likely when using ALS times (95% CI: 5.11–10.33; p<0.05). The absence of mechanical complications, such as catheter occlusion, was another positive effect observed in the patients receiving ALS. The studies included in this meta-analysis used different concentrations of different substances, including gentamicin, minocycline, citrate, taurolidine, cefotaxime, and cefazolin. The major limitation of this review was the relatively short duration of follow up of the included studies, which did not allow for the opportunity to assess long-term adverse events, such as development of antibiotic resistance and systemic toxicity.

Yahav et al.[37] conducted a systematic review of 16 randomised controlled trials that compared single or combination antimicrobial catheter lock solutions with heparin or another antimicrobial for the prevention of infections in HD patients. A total of 11 trials assessed antibiotic catheter lock solutions, 5 trials assessed nonantibiotic antimicrobial catheter lock solutions, and all trials compared the intervention with heparin. The rates of CRB were significantly lower with antibiotic catheter lock solutions compared with heparin lock alone, both per patient (RR: 0.44; 95% CI: 0.38–0.50; p<0.05; all 11 trials included) and per catheter day (RR: 0.37; 95% CI: 0.30–0.47; p<0.05). Catheter removal rates were significantly lower in the intervention group per patient (RR: 0.35; 95% CI: 0.23–0.55; p<0.05; 5 trials; 552 patients) and per catheter day (RR: 0.34; 95% CI: 0.21–0.55; p<0.05; 135,769 catheter days). The emergence of clinically significant resistant strains was reported in 5 trials, including 316 patients receiving intervention and 211 control patients. Only one case of gentamicin-resistant *S. aureus* was reported in a patient receiving gentamicin and citrate during 16 months of follow-up. ESI were reduced in the intervention group but without statistical significance. In studies of nonantibiotic antimicrobial catheter lock solutions, CRB rates were significantly lower with ALS than with heparin alone per patient (RR: 0.46; 95% CI: 0.29–0.71; p<0.05; 4 trials; 642 patients) and per catheter day (RR: 0.48; 95% CI: 0.30–0.76; p<0.05; 60,149 catheter days).

In 2011, Snaterse et al.[38] performed a systematic review with the aim of summarising the evidence on the effectiveness of antibiotic-based catheter lock solutions in preventing BSI in oncology and HD patients and neonates at high CRB risk. Meta-analysis of nine trials showed a significant benefit in favour of the antibiotic-based solutions in HD patients with tunnelled catheters. CRB baseline risk was 3 per 1,000 catheter days, corresponding with a number needed to treat of three patients to prevent one CRB. The authors concluded that to determine the efficacy of the routine use of antibiotic lock solutions in HD patients, other factors should be considered, such as the side effects of antibiotics including the induction of microbial antibiotic resistance and cost-effectiveness.

In 2014, Zhao et al.[39] published a meta-analysis that included 13 randomised studies with 1,770 patients and 221,064 catheter days followed up for 5 years, comparing 4% sodium citrate versus heparin (1,000 U/mL) locks. The rate of CRB was significantly lower in the citrate group (HR: 0.39; CI 95%: 0.27–0.56; p<0.001) when it was associated with other substances, such as gentamicin (p<0.001) or taurolidine (p=0.003).

Taurolidine is a taurine derivative that binds to the wall of bacteria and fungi, promoting the death of these agents. This acts as a disinfectant without inducing bacterial resistance induction.[8] Previous studies have shown that taurolidine has been able to reduce CVC biofilm *in vitro* and *in vivo*.[40,41] In relation to locking prophylactic therapy with taurolidine, two meta-analyses were published between 2013 and 2014. The first included six randomised controlled trials (431 patients, 86,078 day catheters), the use of taurolidine solutions in lock of CVC (HD, nutrition parenteral, and paediatric oncology patients) was significantly associated with a reduction in the incidence of CRB compared to heparin (RR: 0.34; 95% CI: 0.21–0.55; p<0.0001).[42] However, only the reduction in the number of CRB by Gram-negative bacteria was statistically significant with the use of the taurolidine lock (RR: 0.27; 95% CI: 0.11–0.65; p<0.05). There were no differences between groups (taurolidine versus heparin) in relation to catheter occlusion due to thrombosis, with no bacterial resistance to taurolidine in the studies evaluated. However, the authors conclude that the results should be analysed with caution because of the small sample size of the studies and lack of methodological rigor. In 2014, Liu et al.[43] also published a meta-analysis and systematic review comparing locking with taurolidine

versus heparin in patients on CVC and risk of infection (HD patients, paediatric patients with onco-haematological diseases, and use of chemotherapy or parenteral nutrition) with an overall reduction in the incidence of CRB (RR: 0.47; 95% CI: 0.25–0.89; p<0.05) but with no effect on infections caused by Gram-positive bacteria. The incidence of thrombosis differed between the groups with the highest percentage of events in the taurolidine group (RR: 2.11; 95% CI: 1.16–2.09; p<0.05). Due to encompassing only three randomised trials, in addition to the heterogeneity of the study populations, protocols, and results definition, this meta-analysis has limits for interpretation.[43]

Few studies have found the impact of prophylactic lock therapy on CVC in the prevention of catheter ESI. In 2014, a meta-analysis was published of 23 randomised studies, 16 of which were in patients with HD, with a 69% reduction in central-line blood stream infections, defined as the presence of laboratory-confirmed CRB in any patient with CVC at the time or within 48 hours prior to infection, using antimicrobial lock solutions compared to heparin (RR: 0.31; 95% CI: 0.24–0.40; p<0.05) and with a 32% reduction in ESI (RR: 0.68; 95% CI: 0.49–0.95; p<0.05).[44] A possible justification for this effect would be the extravasation that occurs in the CVC, depending on the density of the solution used, type and site of the catheter and position of the body, doses of antimicrobials close to the minimum inhibitory concentration for some pathogens, and consequent systemic maintenance of the subcutaneous tissue near the catheter orifice, reducing ESI rates. There were no differences in all-cause mortality among 13 studies that analysed this outcome (RR: 0.84; 95% CI: 0.64–1.12; p<0.05). The authors also performed sensitivity analyses to assess the effect of lock therapy on centres with low BSI rates, including studies with <1.15 events per 1,000 day catheters (6 trials) and found that the relative rate of BSI reduction remained significant in the subanalysis (RR: 0.32; 95% CI: 0.17–0.60; p<0.05).

Recently, two other meta-analyses were published with different approaches, which also observed the superiority of the substances in lock in relation to rates of catheter-related CRB.

In 2016, Wang et al.[45] published a Cochrane review of 27 randomised studies with a mean follow-up of 6 months, comparing lock therapy with alternative anticoagulant solutions (19 studies with 2,216 patients), systemic anticoagulant agents (6 studies with 664 patients), and lock with low or no dose of heparin (2 studies with 123 patients), mainly with heparin 5,000 IU/mL (used in 17 studies). The primary end point was evaluation of catheter dysfunction, with no statistical difference in the three groups studied. In the individual agent analysis, recombinant tissue plasminogen activator was the only lock solution that showed reduction in catheter malfunction (RR: 0.58; 95% CI: 0.37–0.91; p<0.05).

Regarding the secondary endpoints, there was a significant reduction in CRB rates only in the group with lock of alternative anticoagulant solutions (HR: 0.46; 95% CI: 0.36–0.66; p<0.05), but it was not possible to evaluate CRB in the group with a low or no dose of heparin. In the individual analysis of alternative solutions, except ethanol, all other lock therapies reduced the incidence of CRB (citrate, antibiotics, and recombinant tissue plasminogen activator). However, the interpretation of the evidence from the study is limited by the variations in the interventions tested and the results reported, and randomised trials of high methodological quality are required.

The second study, published in 2017 by Zang et al.,[46] was a meta-analysis that, unlike the others cited, compared the effectiveness of antimicrobial solutions in locking each other in the prophylaxis of catheter-related infections in HD. This Bayesian Network meta-analysis included 18 studies with 2,395 patients and analysed 10 lock therapy strategies (including the control group). Gentamicin + citrate (overall response [OR]: 0.07; 95% CI: 0.00–0.48; p<0.05) and gentamicin + heparin (OR: 0.04; 95% CI: 0.00–0.23; p<0.05) were significantly more effective in reducing rates of catheter-related CRB when compared to the use of heparin-only locks. Regarding the incidence of ESI and all-cause mortality, no significant difference in the intervention effect was detected for all lock solutions when compared to heparin. All solutions were similar for catheter-related CRB, ESI, and all-cause mortality, when compared. This meta-analysis is important to compare the effect of several solutions in locking each other, besides making an analysis of probability of effect among them; however, due to the high

heterogeneity between the studies, a small number of trials evaluated for some of the interventions and methodological quality of the work, the results should be interpreted with caution.

Table 1 summarises the major characteristics of the meta-analysis studies from the last 10 years on prophylactic antibiotic topical and lock therapy for HD-tunnelled catheters.

Table 1: Summary of the meta-analyses using prophylactic antimicrobial therapy in haemodialysis central venous catheters.

Study	Patients	Groups	Results	Adverse events	Strengths and limitations
James et al.,[26] 2008	15 randomised trials 2,395 patients	CG: heparin TG: topical and LS ATB	LS and topical decreased BSI rates Only topical ATB reduced ESI rates 0.06 versus 0.41 ESI per 100 catheter days	NR	LS and topical decreased BSI rates Topical ATB reduced ESI rates
Labriola et al.,[35] 2008	Eight studies N=829 501 TCC 381 NTCC	CG: Heparin TG: Three trials: ATB + heparin Two trials: ATB + citrate Two trials: Citrate without/ATB One trial: ATB+EDTA	LS versus heparin RR: 0.32 95% CI: 0.10–0.42	Dizziness Paraesthesia Metallic taste >Bleeding: heparin versus citrate	LS reduces risk of CRB Adverse events
Jaffer et al.,[36] 2008	Seven studies N=624 448 TCC	CG: Heparin TG: Three trials: ATB + heparin Two trials: ATB + citrate Two trials: citrates/ATB	LS versus heparin 7.72 lower risk 95% CI: 5.1–10.3	Dizziness >Bleeding: Heparin versus citrate	LS reduces risk of CRB Adverse events
Yahav et al.,[37] 2008	Sixteen studies n=924 (lock with ATB) n=661 (lock without/ ATB)	CG: Heparin TG: Six trials: ATB + heparin One trial: ATB One trial: ATB + EDTA Three trials: ATB + citrate TG: Four trials: citrates One trial: citrate + taurolidine	LS versus heparin RR: 0.44 (95% CI: 0.38–0.50) LS versus heparin RR: 0.46 95% CI: 0.29–0.71	ATB group emergency Resistant strains Rash + dizziness <Thrombosis in TG >Bleeding in CG	LS reduces risk of CRB Adverse events
McCann et al.,[27] 2010	10 randomised trials 786 patients	CG: placebo TG: topical mupirocin triple polysporin iodine-povidone honey	Topical drugs versus placebo Mupirocin, triple polysporin, and povidone reduced risk for BSI Only triple polysporin reduced risk for death Honey did not reduce risk for ESI and BSI	NR	Mupirocin, triple polysporin, and povidone reduced risk for BSI

Table 1 continued.

Study	Patients	Groups	Results	Adverse events	Strengths and limitations
Snaterse et al.,[38] 2011	16 studies	CG: Heparin TG (HD): Five trials: ATB + heparin Three trials: ATB + citrate One trial: ATB + EDTA One study in NTCC One study on both Six studies in oncology One study in neonates	ATB versus Heparin Three patients for prevention, one CRB episode	NR	ATB prevention CRB
Zhao et al.,[39] 2014	13 randomised studies 1,770 patients	CG: heparin TG: 4% sodium citrate	Citrate versus heparin HR 0.39, 95% CI: 0.27–0.56	Only when associated with gentamicin or taurolidine	Citrate lock is better than a heparin lock in the prevention of CRB
Liu et al.,[43] 2014	3 randomised trials	CG: heparin TG: taurolidine	Taurolidine versus heparin HR: 0.47, 95% CI: 0.25–0.89	No effect in G+ bacteria >Thrombosis in TG (HR: 2.11, 95% CI: 1.16–2.09)	Taurolidine reduced the risk of CRB Adverse events
Zacharioudakis et al.,[44] 2014	23 randomised trials	CG: heparin TG: ATB solution	ATB LS versus heparin HR: 0.31, 95% CI: 0.24–0.4 (BSI) HR: 0.68, 95% CI: 0.49–0.95 (ESI) Reduction of 69% in BSI and 32% in ES	NR	LS are effective in reducing risk of CRB
Wang et al.,[45] 2016	27 randomised trials	CG: anticoagulant solutions (lock or systemic) TG: ATB solution	ATB LS versus anticoagulant solutions No difference in catheter dysfunction Reduction in BSI only in LS of anticoagulant HR: 0.46, 95% CI: 0.36–0.66	NR	LS of anticoagulant reduced the risk of CRB
Zhang et al.,[46] 2016	18 randomised trials 2,395 patients	CG: heparin TG: LS	LS versus heparin Gentamicin + citrate versus heparin OR: 0.07, 95% CI: 0.00–0.48 Gentamicin + heparin versus heparin OR: 0.04, 95% CI: 0.00–0.23	NR	Gentamicin + heparin may be selected for the prophylaxis of CRB

Table 1 continued.

ATB: antibiotic; BSI: bloodstream infection; CD: catheter day; CG: control group; CRB: catheter-related bacteraemia; CVC: central venous catheter; DS: dialysis session; EDTA: ethylenediaminetetraacetic acid; ESI: exit site infection; LS: lock solution therapy; MuRSA: mupirocin-resistant *Staphylococcus aureus*; NR: not reported; NTCC: non-tunnelled central venous catheter; TCC: tunnelled central venous catheter; TG: treatment group; tPA: tissue plasminogen activator.

CONCLUSION

Although recent meta-analyses have shown favourable results related to the use of antimicrobial lock therapy in reducing the rates of catheter-related infection, the 2006 NKF KDOQI guidelines still do not recommend ALS or topical antibiotic for the prophylaxis of CRB in patients on HD.[7] According to the 2011 CDC guidelines, their use should be reserved to patients with a long-term catheter, who have a history of multiple CRB, despite optimal maximal adherence to aseptic techniques.

As final recommendations based on several studies discussed, topical antibiotics and catheter lock solutions are the primary means of preventing BSI and should be used, but the risk of emergence of organisms resistant to the antibiotics used should be considered. Further studies to assess the impact of long-term use of intraluminal and topical antimicrobial on the development of bacterial resistance are warranted.

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