Review Article

Recent Advances in Nephrology: The Research Gaps and the Need for Greater Emphasis on Incorporating Hard Clinical Endpoints

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Abstract

Current limitations exist in the availability of specific therapies for preventing acute kidney injury (AKI). Managing AKI poses challenges, particularly as interventions are often initiated only after a substantial increase in serum creatinine or a gradual decline in urine output. However, relying on these parameters raises concerns due to their insensitivity to acute changes. The timely detection of patients at risk of kidney disease through the diagnostic utility of biomarkers is essential for the prompt implementation of active interventions. Despite the initial optimism surrounding the discovery of AKI biomarkers, their integration into the routine care of at-risk patients lags behind and is underutilized, even after validations. Therefore, the utilization of biomarkers holds promise in promptly diagnosing AKI and improving patient outcomes. Despite notable technological advancements in various medical subspecialties, survival rates among acute and chronic kidney disease (CKD) patients have not witnessed significant improvement compared to other disciplines. While HIV infection and AIDS were once considered a death sentence, advancements in HIV treatment have allowed for control and longer-acting management. However, a definitive cure for CKD remains elusive. Nephrology research faces challenges, including the imperative to enhance both the quality and quantity of research. The number of randomized controlled trials in nephrology is notably lower compared to other subspecialties, with many yielding negative results. Studies evaluating hard clinical endpoints are also limited. This review provides an overview of recent advances in nephrology and the need for greater emphasis on incorporating hard clinical endpoints that could impact clinical practice.

Keywords: *Clinical endpoint, kidney disease studies outcome, nephrology research*

Introduction

Acute kidney injury (AKI) is associated with increased morbidity, mortality, healthcare costs, and the risk of long-term complications.[1] The reduction in glomerular filtration rate over a short period serves as the defining feature of AKI.[2] The occurrence of AKI has been correlated with an increased risk of progressive chronic kidney disease (CKD),[3] end-stage kidney disease (ESKD),[4] and cardiovascular disease.[5] Among critically ill patients, the reported incidence of AKI is as high as 50%, with 10% requiring acute renal replacement therapy (RRT).[6,7] Despite significant progress in critical care nephrology research over the past few decades, clinical practices have not kept pace, and the contributions of biomarkers remain incompletely defined.

Earlier studies spanning several decades elucidated the role of continuing vasoconstriction, tubular

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occlusion, cellular structural and metabolic alterations, and inflammatory responses in the pathogenesis of AKI.[8] While these studies paved the way for successful therapeutic approaches in animal models, translational efforts in humans have not yielded tangible results.[8] The slow progress is attributed to various factors, including the kidney's response to nephrotoxic injury, a lack of early biomarkers of kidney injury, the prototype of troponins in myocardial injury, and the need to enhance the quality and quantity of randomized controlled trials (RCTs), with scarce studies evaluating hard clinical endpoints.[8]

Current diagnostic practices for AKI rely on the rise in creatinine and/or a decrease in urine output over time.[9] However, concerns exist regarding the use of serum creatinine as a standard biomarker of kidney injury due to its insensitivity to acute changes and wide variability influenced by age, gender, muscle mass, diet, medications, and hydration status.[10] Timely diagnosis and management of AKI are crucial to prevent irreversible damage and poor outcomes.[8] While animal studies demonstrated that AKI due to nephrotoxins is potentially preventable and treatable with early interventions,[11] effective curative therapy for AKI in humans is currently lacking, and treatment options are predominantly supportive.[12] Although RRT is integral to AKI management, concerns persist, including controversies around the appropriate timing of initiation and completion, with survival remaining a paramount concern.[13] The diagnostic utility of biomarkers for early detection in patients at risk of kidney disease is crucial for the timely implementation of active intervention bundles. Despite the initial disillusionment in AKI biomarker research, the discovery of biomarkers has reignited interest. Therefore, we discussed the recent advances in nephrology practice with a greater emphasis on the need for incorporating hard clinical endpoints as priorities and highlighted the major obstacles that slowed the progress of research implementation in clinical practice.

Methodology

The electronic databases, PubMEd, Scopus, and Web of Science, from 2001 to 2015 were searched using keywords: Nephrology, Cardiology, Endocrinology, Gastroenterology, Hematology, Oncology, Pulmonology, Rheumatology, and Infectious Diseases. One hundred abstracts were used to identify potentially relevant studies. Also, full texts of studies that passed the relevant screening were used. RCTs that evaluated the effectiveness of interventions in the population were included. Studies published in languages other than English were excluded. A standard form was used to extract data including study characteristics, population, demographics, intervention details, and outcome measures. Three reviewers extracted data independently. Finally, 60 published papers including abstracts were used for the study.

Validation of biomarkers for early AKI detection

In 2014, the Food and Drug Administration (FDA) announced the marketing of the NephroCheck test, designed to identify critically ill patients at risk of developing AKI within 12 hours. This test assesses urinary concentrations of Tissue Inhibitor of MetalloProteinase 2 (TIMP2) and Insulin-like Growth Factor-Binding Protein 7 (IGFBP7), biomarkers of cell cycle arrest. A multicenter cohort study (SAPPHIRE) conducted by Kashani *et al*.[14] identified the combination of urinary TIMP2 and IGFBP7 as a promising predictor of moderate to severe AKI in critically ill patients. Subsequent validation in the Tolvaptan Outcome Project Altruism in Zerenex (TOPAZ) cohort further supported the clinical utility of these biomarkers.[15] Several studies have since utilized these biomarkers to predict AKI in various settings, such as cardiac surgery.[16] Despite the initial disappointment in AKI biomarker research, their implementation in routine care for high-risk AKI patients remains an active area of investigation.

Neutrophil Gelatinase-Associated Lipocalin (NGAL) as a unique biomarker for AKI risk prediction

Recent advancements in functional genomics have facilitated efforts to decipher the molecular basis of early kidney responses to injury. These breakthroughs, particularly in genomewide analysis of complex biological processes like nephrotoxic AKI, have made the task more accessible.[17] Among the identified genes, NGAL has emerged as a prominent candidate, serving as an early biomarker in both urine and plasma for AKI.[18] Originally recognized as a 25 KDa protein involved in innate immunity and antibacterial defense released by activated neutrophils, NGAL is also produced by renal tubular cells in response to various injuries.[18] A study by Haase-Fielitz *et al*.[19] strongly supports the use of serum NGAL and urinary NGAL as biomarkers in predicting AKI related to cardiac surgery, critical illness, and kidney transplantation. In cases of post-nephrotoxic injury, NGAL undergoes significant upregulation in multiple nephron segments, concentrating predominantly in the proximal tubule where it colocalizes with proliferating epithelial cells.[18] Observations from clinical studies have established NGAL as a reliable predictor of AKI, with evidence suggesting that NGAL induction represents a novel intrinsic response of kidney

proximal tubule cells to nephrotoxic injury, distinct from its origin in activated neutrophils. The rapid appearance of NGAL in urine within 2 hours of injury makes it a valuable tool for early detection of renal tubular injury, preceding changes in creatinine levels.[20]

Human serum NGAL levels show a substantial increase, up to 16-fold, reflecting the severity of injury, while urinary levels increase from 25- to 100-fold.[21] This led to the development of NGAL assays for the early detection of renal tubular injury in humans. Notably, NGAL levels in urine and plasma rise before any increase in creatinine levels, serving as a more reliable predictor of AKI.[22] In patients with CKD associated with conditions like polycystic kidney disease, glomerulonephritis, and diabetic nephropathy, NGAL levels correlate with the extent of kidney damage and independently correlate with the glomerular filtration rate.[23] In critically ill patients, NGAL measurement holds significant prognostic value, predicting the risk of disease progression to CKD in the short to medium term.[24] One of the drawbacks, however, is that biomarkers of kidney disease may not always correlate well with the severity of the disease, so they may not be very useful for monitoring of the progression of the disease.

Development of clinical AKI risk prediction models in critical care nephrology

In recent years, critical care nephrology has witnessed the emergence of various validated clinical AKI risk prediction models, marking significant progress in the field. Basu *et al*.[25] introduced the renal angina index (RAI), combining risk criteria and injury criteria in critically ill children. Malhotra *et al*.[26] developed a risk score for critically ill adults, while Flechet *et al*.[27] created the AKI predictor tool using machine learning. Despite these advancements, further validation in multicenter cohorts and the inclusion of novel biomarkers are necessary to enhance the performance of these prediction models.

Prevention of AKI and development of AKI therapeutics

Preventing AKI remains a challenge, with specific treatments unavailable. Renoprotective measures such as avoiding nephrotoxic drugs and optimizing hemodynamic status have shown promise in preventing AKI in high-risk groups.[28] The AKI trial demonstrated a significant decrease in postoperative AKI incidence with the implementation of the KDIGO bundle.[25] Additionally, angiotensin II is a newly approved drug for septic or distributive shock, which showed an improvement from RRT in a *post hoc* analysis of AKI patients.[29,30]

Impact of Nephrology Research on Clinical Practice

Magnitude of clinical trial in nephrology and other subspecialties of internal medicine We utilized the Pubmed medical subjects' headings to identify categories for exploration within eight primary subspecialties of internal medicine: cardiology, endocrinology, gastroenterology, oncology and hematology, infectious disease, pulmonology, and nephrology. Our data search, covering up to 2018, revealed ongoing inclusion of information from 2016, 2017, and 2018 publications. To avoid incorporating potentially incomplete data, we chose to conclude our analysis with data up to 2015. In 2001, the number of clinical trials (CTs) in nephrology was 193, and this figure increased to 601 by 2015. This trend was generally observed across most subspecialties [see Figure 1]. Notably, both nephrology and rheumatology had the lowest publications indexed in Pubmed compared to other subspecialties. Over the period from 2001 to 2015, cardiology exhibited approximately eight times more published papers than nephrology. This discrepancy remained consistent over time [see Figure 2].

Despite significant advancements in various medical fields, particularly in reducing myocardial infarction, stroke, and overall mortality rates in the general population, the survival rates for patients with kidney failure have not shown substantial improvement over the same period. In the United States, the expected lifespan of dialysis patients aged 60–64 years is approximately 4.5 years, a figure comparable to that of patients with lung cancer.[31] In contrast, developing countries are grappling with a dual burden of disease, facing both communicable and noncommunicable health challenges.[32]

A few decades ago, HIV infection and AIDS were considered as a death sentence. However, the landscape changed dramatically with progress in HIV treatment, transforming the outlook for patients from the fear of sudden death to the possibility of prolonged living. Ongoing research is pushing the boundaries of treatment, aiming for longer-acting therapies and even potential cures. Similarly, advancements in cancer research have made the once seemingly impossible goal of curing certain malignancies a reality.

The Advocacy Committee of the American Society for Nephrology (ASN) estimated that the National Institutes of Health (NIH) allocates over $500 for research per cancer patient and $2500 per individual with HIV infection. In contrast, the NIH dedicates a mere $30 annually for each patient with CKD. In 2015, Medicare

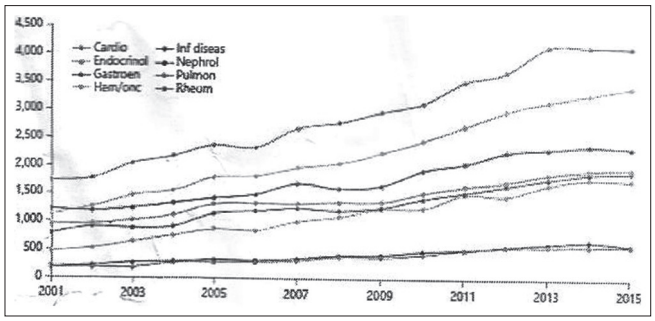

Figure 1: The number of funded research articles published and indexed in PubMed for Nephrology and other subspecialties of internal medicine 2001-2015
Cardio - cardiology, Endocrinol-Endocrinology Gastroen-Gastroenterology, Ham-Heamatology
Onc-Oncology, Inf disease-Infectious disease, Nephrol –Nephrology, Pulmon-Pulmonology, Rheom-Rheomatology

spent nearly $34 billion on ESKD patients, while the NIH allocated only $564 million to kidney disease research in the same year. With less than 2% of the cost of care directed toward kidney research, it is not surprising that healthcare progress in HIV and cancer has outpaced that of kidney disease in recent years.

COVID-19 Pandemic Outbreak and Consequences

In March 2020, the World Health Organization (WHO) declared the outbreak of the novel coronavirus (COVID-19) a global emergency, marking the beginning of a pandemic with profound consequences worldwide. Initial data from Johns Hopkins University (JHU) estimated that over 1.7 million people were infected within the first month, resulting in 80,000 fatalities, with USA reporting over 2000 deaths within 24 hours. Elderly individuals with underlying health conditions, particularly those with a compromised immune status, bore a disproportionate burden of vulnerability.

Experts recommended various measures to curb the spread of the virus, including personal hygiene practices like handwashing, the use of alcohol-based sanitizers, wearing face masks, practicing social distancing, and implementing lockdown. The FDA, on April 16, 2020, encouraged COVID-19 survivors to donate blood to assist those with complications, although no specific therapeutic agents had yet undergone clinical trials. The shortage of medical equipment, such as ventilators for intensive care units, further strained healthcare systems, leading to health and economic crises, particularly in less affluent countries.

Amid this global health emergency, CKD, an ongoing global health challenge with no cure, continued to contribute to fatalities worldwide. As of January 2023, coronavirus disease (COVID-19) has been estimated

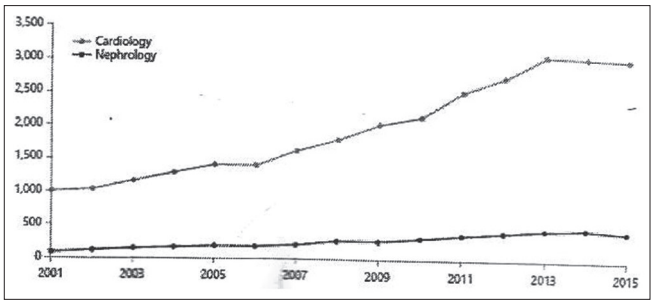

Figure 2: Comparison of Published papers in Nephrology with cardiology. (Adapted from Yasan *et al*. Kidney disease 2019:5:69-80)

to have caused 6 million deaths worldwide.[33] Patients with CKD had a five time greater risk of severe COVID-19 infection than the general population due to their immunosuppressed state and chronic systemic inflammation.[34] Acknowledging the devastating impact of COVID-19, the nephrology community must develop response strategies that are comprehensive and tailored to meet the needs of entire populations. If kidney research initiatives gain momentum in terms of both quality and quantity, with the discovery of clinical endpoints, it is hoped that such progress may expedite the development of new technologies for managing kidney disease patients and improving outcomes. It is imperative to prevent the world from experiencing another health crisis on the scale of COVID-19.

Kidney disease initiative global outcome (KDIGO 2017)

The initial KDIGO guideline, primarily based on observational data and expert opinion, prompted widespread changes in clinical practice. In 2017, a selective update was published,[35] recommending a more individualized approach to managing chronic kidney disease–mineral bone disorder (CKD-MBD) due to the lack of proven benefits for intermediate biochemical and cardiovascular endpoints. However, concerns were raised about the potential overuse and misuse of certain treatments, leading to adverse metabolic consequences such as hypercalcemia. Many recommendations in the updated 2017 KDIGO guideline continue to be debated due to the insufficient evidence supporting various recommendations in CKD-MBD management.

A significant challenge in the updated 2017 KDIGO guideline lies in the use of bone mineral density (BMD) testing to assess fracture risk in CKD stages 3a-5D. Although prospective cohort studies demonstrated that BMD measurement predicted fractures in this population,[36,37] the guideline introduces uncertainty and does not offer clear advice on how to treat low BMD in CKD patients, who are often excluded from most RCTs. The language used in the updated CKD-MBD guideline lacks specificity, with recommendations often qualified

by phrases like "we suggest" or "we recommend," and the majority are supported by very low levels of evidence. The reason for the nonstrong recommendation by KDIGO is due to inadequate evidence, thus supporting the need for more research in nephrology. The absence of actionable recommendations underscores the challenges in implementing and disseminating information, emphasizing the importance of clinical judgment in conjunction with guidelines.

The PRIMO trial, investigating the impact of paricalcitol on the left ventricular mass index and measures of diastolic dysfunction,[38] did not show a significant effect on the primary endpoint, leaving clinicians with challenging decisions. The Rheos pivotal trial, a large-scale double-blinded placebo-controlled RCT evaluating baroreflex activation therapy, demonstrated sustained efficacy benefits but did not meet the primary endpoint of lowering blood pressure.[39] Similarly, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial found no renal or cardiovascular benefits of renal artery stenting in advanced hypertensive CKD patients with more than 60% renal artery stenosis.[40] These outcomes highlight the complexities and uncertainties in CKD-MBD management and emphasize the urgent need for higher-quality research in this field.

Glycemic Control on Renal Outcomes in Type 2 Diabetes

While tight glycemic control has demonstrated positive outcomes in diabetic patients with early CKD, there is a scarcity of data supporting the benefits of intensive glycemic control for those with advanced CKD. The United Kingdom Prospective Diabetes Study (UKPDS) examined the impact of glycemic control on the risk of microvascular and macrovascular complications in type 2 diabetes patients.[41] Tighter blood control was associated with a reduced risk of microvascular disease, but it also led to an increased risk of hypoglycemia and weight gain, with no significant effect on macrovascular complications. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, focusing on aggressive glycemic control with an HbA1c target of <6%, resulted in increased mortality and did not significantly reduce major cardiovascular events. The ADVANCE trial provided a more optimistic perspective, indicating benefits from tight blood sugar control.[42] The tightly controlled group exhibited a reduced risk of developing microalbuminuria as well as a slowdown in the progression of macroalbuminuria and the risk of ESKD. However, the low number of patients developing ESKD (0.24%) raises some uncertainty in the findings.[42] While there was no significant effect on serum creatinine over time, a nonsignificant trend toward more frequent doubling of serum creatinine was observed in the tightly treated group. To date, no trial has convincingly demonstrated a beneficial effect of tight therapy on macrovascular outcomes in individuals with long-standing type 2 diabetes. A recent abstract presented by the TSUBAKI study group at the American Society of Nephrology annual meeting reported that bardoxolone improved renal function, as assessed by insulin clearance, in diabetic patients with stage 3 and 4 CKD within a preselected cohort, without identifying risk factors associated with fluid overload.[43]

Risk and Benefits of Antihyperkalemia Treatments

Hyperkalemia is prevalent in individuals with kidney diseases, especially those with a low glomerular filtration rate. Various therapeutic options have been reported.[44] Patients with advanced CKD and ESKD who encounter elevated potassium levels are commonly advised to adhere to low-potassium diets. However, there is a lack of randomized evidence to ascertain the effectiveness of this approach, and it remains a necessary area for investigation. It has been noted in a report that an unintended consequence of this dietary advice might be a shift toward lower dietary quality. This aspect should be specifically scrutinized in any trials of dietary intervention, considering factors such as dietary satisfaction, patient experience, costs, illness intrusiveness, and abdominal side effects. In October 2018, a multidisciplinary group of researchers and clinicians convened to address controversies and identify evidence in potassium management. However, evidenced-based recommendations on preferential strategies were challenging due to the lack of evidence for most strategies, the absence of evidence on the comparative efficacy of alternative strategies, and the potential for harm with at least some of them.[45] This underscores the urgent need for higher-quality research in kidney disease to drive innovation and develop new technologies for managing kidney disease patients and improving outcomes.

The report proposes that outpatients with acute hyperkalemia, presenting with a potassium level of >6.0 mmol/L or hyperkalemia accompanied by any ECG changes, should be referred to a cardiac monitoring unit in an emergency setting that can promptly address the issue. This suggestion is based on clinical recommendations.[46,47] However, it acknowledged that most evidence has been produced in a convenient sample of stable predialysis patients with hyperkalemia and that the synthesis into an algorithm has not been rigorously

tested. The report further advised repeating potassium levels to rule out pseudohyperkalemia or considering clinical judgment and the presence of ECG changes to balance the importance of verification against the delay of treatment.

Metabolic acidosis

Due to the loss of functioning nephrons, patients with CKD experience positive net acidosis, with serum bicarbonate (HCO3-) levels below 22 mmol/L, being one of the earliest and most insidious indicators.[48] Despite this, only a limited number of RCTs have been published investigating the effects of correcting metabolic acidosis in a relatively small patient population. The KDIGO guideline suggests that individuals with CKD having serum bicarbonate concentrations below 22 mmol/L should receive oral bicarbonate supplementation to maintain serum bicarbonate within the normal range, unless contraindicated.[49] However, this guideline is classified as a suggestion rather than a recommendation (Level 2B) due to a lack of robust evidence.

In a single-blind controlled trial involving 46 patients, Mathur *et al*.[50] found that correcting metabolic acidosis was associated with a reduction in the rise of blood urea and parathyroid hormone levels, though it did not impact other metabolic parameters related to CKD-MBD. Another study by De Brito-Ashurst *et al*.[51] reported that correcting metabolic acidosis could slow the progression of CKD and the need for dialysis. Although this trial was the largest RCT published on correcting metabolic acidosis in CKD patients, it was a single-center open-label study involving only 134 patients. The question arises as to why there is a lack of well-designed RCTs with larger patient cohorts addressing the metabolic acidosis in CKD patients.

Glomerulonephritis Treatment

The diagnosis and treatment of glomerulonephritis (GN) represent one of the rapidly advancing areas in nephrology. Idiopathic membranous nephropathy (IMN) is diagnosed based on the presence of the glomerular subepithelial antigen–antibody immune complex, with the composite known as IgG4 antibody binding to the phospholipase A2 receptor (PLA2R) in podocytes.[52] Circulating PLA2R antibody levels in IMN correlate well with disease activity and contribute significantly to understanding the disease and monitoring response to immunosuppressive treatment.[53] Rituximab, as a first-line treatment for IMN, induces remission and significantly improves glomerular filtration rates (GFRs) in patients who achieve complete remission, with transient and well-tolerated adverse effects that are not serious.[54]

Ongoing multicenter RCTs on IMN, such as MENTOR and STARMEN, brought optimism to nephrology researchers. The MENTOR trial, a noninferiority study, compares rituximab with cyclosporine,[55] while the STARMEN trial investigates the efficacy of sequential treatment with tacrolimus-rituximab versus steroids plus cyclophosphamide.[56]

In a phase 2 RCT, fresolimumab, a monoclonal anti-transforming growth factor-beta antibody, did not meet primary endpoints in patients with steroid-resistant FSGS.[57] Abatacept, another costimulatory inhibitor targeting B7-1, successfully induced complete or partial remission in five patients with primary FSGS.[57] Encouraged by these results, ongoing phase II RCTs are studying the effects of abatacept in patients with resistant FSGS.[58] While significant advances have been made in understanding the pathophysiology of GN, leading to new treatment strategies, the lack of larger RCTs in this field emphasizes the pressing need for more research in this area.[59]

Conclusion

Some of the recent advances in nephrology include the development of new biomarkers that are more specific for kidney disease and have better correlation with disease severity. For example, there has been increasing interest in biomarkers such as Cystatin C and NGAL, which showed promise as a more accurate biomarker of kidney function. In addition to biomarkers, there are several other advances that are worth mentioning. There are newer classes of medications such as Sodium-Glucose Linked Transporter 2 (SGLT2) inhibitors and Renin-Angiotensin-Aldosterone System (RAAS) inhibitors that can slow the progression of kidney disease. Another advance is the use of artificial intelligence to improve the diagnosis and treatment of kidney disease. Also, there has been increasing research into the role of lifestyle factors. The lack of clear clinical endpoints is a significant challenge in the treatment of CKD. The most commonly used clinical endpoints such as glomerular filtration rate and protenuria are not always well correlated with patient-reported outcomes such as quality of life. A few clinical trials have been conducted in Africa, especially Nigeria. Oversight agency in the particular country, National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria, and Food and Drug Administration (FDA) in USA should have a leading role in clinical trial and approval. Therefore, there is a need for more research and funding in order to incorporate hard clinical endpoints in nephrology practice.

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Conflicts of interest

There are no conflicts of interest.

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