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Emerging trends in renoprotective agents; a pharmacological perspective for world kidney day 2025

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ABSTRACT

The management of kidney disease is witnessing a paradigm shift, driven by the emergence of innovative renoprotective agents and a deeper understanding of disease mechanisms. This review highlights the latest pharmacological advancements and therapeutic strategies aimed at preserving renal function and improving outcomes for patients with kidney disease. Key developments include the exploration of cell therapy and regenerative medicine, particularly the use of renal progenitor cells to repair damaged kidney tissue, and the groundbreaking application of kidney organoids, which offer new insights into disease pathology and personalized treatment approaches. Additionally, the shift toward combination therapies, such as the concurrent use of SGLT2 (sodium-glucose cotransporter 2) inhibitors with other kidney-protective agents, demonstrates significant promise in addressing the multifactorial nature of kidney disease progression. Beyond pharmacological interventions, the integration of lifestyle modifications, including dietary adjustments, physical activity, and risk factor management remains fundamental to both prevention and treatment. As we commemorate world kidney day, this review also emphasizes the importance of a multidisciplinary approach, combining cutting-edge pharmacological innovations with holistic lifestyle strategies to combat the global burden of kidney disease and improve patient outcomes.

Review

Implication for health policy/practice/research/medical education:
The global burden of kidney disease represents a critical public health challenge that demands immediate attention and coordinated action. The combination of increasing prevalence, economic burden, and healthcare disparities creates a complex challenge that requires innovative solutions and global collaboration. As we move forward, addressing this crisis will require a multi-layered approach that combines access to care, development of novel therapeutics, and attention to environmental and also social determinants of health. Success in reducing the global burden of kidney disease will depend on sustained commitment from healthcare providers, policymakers, and the international community to implement comprehensive strategies that address both prevention and treatment while ensuring equitable access to care for all populations..

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Introduction

The establishment of world kidney day represents a landmark initiative in global health advocacy, marking a significant shift in how the international community approaches kidney disease awareness and treatment (1). Since its inception in 2006, this global campaign has evolved from a modest beginning with 66 participating countries to become a powerful worldwide movement that unites healthcare professionals, researchers, and advocates in the fight against kidney disease (1). This transformation reflects growing recognition of kidney disease as a critical public health challenge that demands innovative therapeutic solutions and coordinated global action. World kidney day has emerged as a catalyst for advancing kidney health awareness and therapeutic development, particularly as chronic kidney disease affects more than 850 million people worldwide and resulted in over 3.1 million deaths in 2019 (2). The campaign's impact extends beyond mere awareness, serving as a platform for highlighting critical developments in kidney disease treatment and prevention. Over the last recent decades, treatment efforts primarily focused on kidney replacement

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therapies; however, recent therapeutic breakthroughs have opened unprecedented opportunities to prevent or delay disease progression and mitigate complications (2,3). Additionally, the landscape of kidney disease treatment has witnessed remarkable advancement, with new therapeutic agents showing promising results in delaying kidney function decline. Notably, recent developments in pharmacological interventions, including renin-angiotensin inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, non-steroidal mineralocorticoid receptor antagonists (MRAs), and GLP-1 receptor agonists, have demonstrated significant benefits in improving patient outcomes (4), though these therapeutic advances face substantial implementation challenges. Barriers such as lack of chronic kidney disease (CKD) awareness, insufficient knowledge of newer therapeutic strategies and treatment costs contribute to the profound disparities in accessing treatments, particularly in low-and-middle-income countries (5). World kidney day has increasingly focused on addressing healthcare disparities in kidney disease treatment (2). The stark reality is that, many countries still lack access to basic diagnostics, a trained nephrology workforce, and universal access to primary health care. This disparity is particularly evident in these countries, where only 12% have access to serum creatinine measurement and glomerular filtration rate assessment at the primary care level (6). Addressing these problems requires a multi-faceted approach that combines improved healthcare infrastructure, workforce development, and innovative solutions for treatment delivery. The annual observance of world kidney day has catalyzed research and development efforts in nephrology. Through coordinated global campaigns and themed initiatives, the event has helped highlight critical areas requiring therapeutic innovation (7). The 2024 campaign theme, "Kidney Health for All — advancing equitable access to care and optimal medication practice," exemplifies this focus on therapeutic advancement while emphasizing the importance of equitable access (2). World Kidney Day 2025 will also be observed on March 13, featuring the theme "Are Your Kidneys, OK? Detect Early, Protect Kidney Health." The WKD campaign emphasizes on critical importance of early detection and intervention in preventing and managing kidney disease, which can significantly improve health outcomes (7). This approach has encouraged researchers and pharmaceutical companies to develop more effective and accessible treatment options while considering the global context of their implementation. Recent advances in diagnostic capabilities present new opportunities for early disease detection and intervention. The development of non-invasive testing methods, such as AI-powered retinal scans for predicting CKD risk, represents a significant breakthrough in disease screening and risk assessment (8). Additionally, new predictive tools like the Klinrisk model, which utilizes routine laboratory measurements to forecast disease progression, offer promising approaches for early intervention and improved patient outcomes (9). Looking ahead, world kidney day continues to evolve in response to emerging challenges and opportunities in kidney health. The focus increasingly extends beyond traditional therapeutic approaches to encompass broader health system challenges. This focus also includes addressing climate change impacts on kidney health, developing innovative solutions for disaster preparedness, and leveraging digital transformation to advance healthcare delivery. These emerging focus areas reflect the campaign's adaptability and commitment to address both current and future challenges in kidney disease treatment.

Search strategy

For this study, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, using different keywords including; world kidney day, kidney disease, sodium-glucose co-transporter 2 inhibitors, therapeutic agents, early diagnosis and SGLT2 inhibitors.

Global burden of kidney disease and need for renoprotective strategies

Chronic kidney disease represents a significant and growing global health crisis, affecting approximately 850 million people worldwide, with most patients residing in low-income and lower-middle-income countries (10). This devastating condition imposes substantial burdens on patients and healthcare systems with its prevalence increasing at an alarming rate. Currently, kidney disease is the third fastest-growing cause of death globally and notably stands as the only non-communicable disease exhibiting a continued rise in age-adjusted mortality (11). The clinical burden of kidney disease manifests through various stages and complications, creating a complex web of health challenges (12). According to recent data, the global median prevalence of CKD is 9.5%, with significant variations across regions (13). The economic implications are equally staggering, with annual direct costs per patient increasing dramatically as the disease progresses. Indeed, early-stage management costs approximately $3060 annually, while advanced stages requiring dialysis can exceed $57 334 per year (14). This economic burden particularly affects developing nations, where healthcare systems struggle to provide adequate support for patients requiring kidney replacement therapy (14). A troubling aspect of the global kidney disease crisis is the profound disparity in access to care. In resource-poor settings, as many as nine out of ten individuals with CKD remain unaware of their condition, leading to delayed diagnosis and treatment (10,15). The situation is particularly harmful in low-income and middle-income countries, which have only 7% of the global kidney replacement therapy population despite comprising 48% of the world population (10). These disparities are further exacerbated

by social determinants of health, with factors such as gender, race, and ethnicity significantly influencing both the risk of kidney disease and health outcomes (16). The burden of kidney disease is increasingly linked to environmental and social factors. Climate change and environmental degradation pose growing threats to kidney health, with evidence suggesting that persistent exposure to high temperatures, particularly among agricultural workers in low-income countries, increases the risk of kidney disease (17,18). Furthermore, the rise in environmental toxins, air pollution, and declining biodiversity creates additional challenges, especially for vulnerable populations lacking resources for adaptation and mitigation (10). The current therapeutic approach to kidney disease primarily centers on controlling blood pressure and managing diabetes, yet these interventions alone prove insufficient (19). Traditional renoprotective therapies, while valuable, leave considerable room for innovation (20). The development of new treatments faces significant obstacles, including slow patient enrollment in clinical trials, regulatory requirements for hard patient outcomes, and limited payer engagement (21). These challenges particularly affect developing countries, where access to even basic kidney care remains limited. Recent advances in therapeutic approaches offer promising directions for addressing the global burden of kidney disease (22). The development of sodium-glucose cotransporter 2 inhibitors and novel MRAs presents new opportunities for treatment (23). Additionally, increasing attention to early detection and prevention strategies, coupled with improved understanding of disease mechanisms through metabolomics, offers potential pathways for reducing the disease burden (24).

The evolution of traditional renoprotective approaches: from ACE inhibitors to modern therapeutics

The course of renoprotective therapy has been fundamentally shaped by the introduction and widespread adoption of agents targeting the renin-angiotensin-aldosterone system (RAAS) (25). Since their introduction in the early 1980s, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have emerged as cornerstone therapies in nephrology, offering substantial benefits for patients with various forms of kidney disease (26). These agents have demonstrated remarkable efficacy in protecting glomerular function and reducing albumin excretion, establishing themselves as essential components of modern kidney disease management (20). The therapeutic potential of RAAS blockade emerged from a deep understanding of the complex pathophysiology underlying kidney disease. ACE inhibitors act by preventing the conversion of angiotensin I to angiotensin II, while ARBs block the receptors that angiotensin II typically acts upon (27). This dual approach to RAAS modulation has proven particularly effective in managing hypertension and protecting kidney function. The mechanism of their efficacy is attributed to the relaxation of blood vessels and reduction of pressure within the kidneys, finally leading to improved outcomes in patients with CKD (28). The implementation of ACE inhibitors and ARBs has revolutionized the treatment landscape for various renal conditions. These agents have demonstrated significant efficacy in managing diabetic nephropathy, reducing proteinuria, and slowing the progression of CKD (29). Clinical evidence has consistently shown that, these medications can delay the progression of nephropathy and reduces cardiovascular events in both hypertensive and normotensive patients with diabetes mellitus (30). Furthermore, their renoprotective benefits extend beyond blood pressure control, offering organ protection through multiple pathways. Despite their established benefits, traditional renoprotective approaches face several significant limitations (27). The effectiveness of ACE inhibitors and ARBs can be compromised by various factors, including angiotensin and aldosterone breakthrough. These phenomena may limit the long-term efficacy of these agents in some patients (31). Additionally, the risk of hyperkalemia, particularly in patients with advanced kidney disease, necessitates careful monitoring and may restrict dosing (32). The potential for acute kidney injury, especially when combined with certain medications or in the setting of volume depletion, represents another important consideration in the clinical practice of these medications (33). Hence, the increasing prevalence of CKD, coupled with limited treatment options, has created an urgent need for novel therapeutic agents. Chronic renal failure is a 'disease multiplier,' affecting multiple organ systems and complicating patient care (34). Recent developments in understanding kidney disease pathophysiology have opened new modalities for therapeutic intervention (35).

The development of SGLT2 inhibitors marks a revolutionary advance in kidney disease therapy (36). Originally developed for glycemic control, these agents have demonstrated remarkable efficacy in preventing kidney disease progression through mechanisms independent of their effects on blood glucose (36). The primary mechanism involves reducing glomerular hypertension through tubuloglomerular feedback, leading to decreased intra-glomerular pressure and subsequent protection of kidney function (37). This hemodynamic effect represents a fundamental shift in therapeutic approach, moving beyond traditional paradigms of blood pressure control and RAAS blockade (38). Clinical evidence supporting the efficacy of SGLT2 inhibitors has been particularly compelling. As an example, the CREDENCE trial demonstrated a 30% reduction in the composite risk of kidney failure, doubling of serum creatinine, or death from kidney or cardiovascular causes in patients treated with canagliflozin (39). Similarly, the DAPA-CKD trial showed that dapagliflozin reduced the primary composite outcome by 39% in patients with

chronic renal failure, regardless of diabetes status. These findings have established SGLT2 inhibitors as essential components of modern kidney disease management (40). Accordingly, MRAs have emerged as a promising therapeutic class, particularly in addressing the residual risk that persists despite optimal standard therapy. These agents act through multiple mechanisms, including anti-inflammatory and antifibrotic effects (41). The evolution of MRA therapy has progressed from traditional steroidal agents like spironolactone to newer, non-steroidal selective antagonists that offer improved tolerability profiles (42). Recent evidence has demonstrated that MRAs can significantly reduce proteinuria and slow the progression of kidney disease (43). Studies indicate that the addition of MRA therapy to standard treatment results in substantial reductions in albuminuria, particularly in patients with diabetic kidney disease (44,45). In addition, the emerging role of metabolic modulators represents a novel approach to kidney disease treatment, focusing on fundamental cellular energy pathways. Prior investigations have detected that metabolic dysfunction plays a crucial role in both acute and CKD, particularly in the disruption of fatty acid oxidation and glycolysis (46). Metabolic reprogramming in kidney disease involves complex interactions between various pathways, including fatty acid oxidation, glycolysis, and the tricarboxylic acid cycle (46,47). The proximal tubule, with its high energy demands, is particularly susceptible to metabolic perturbations, making it an important target for therapeutic intervention (47). Recent clinical trials have provided robust evidence supporting the efficacy of these novel therapeutic classes. The EMPA-KIDNEY trial demonstrated significant benefits of empagliflozin in patients with CKD, including those without diabetes (48). Besides, a systematic review and meta-analysis of 13 trials involving over 90 000 participants confirmed that SGLT2 inhibitors reduced the risk of kidney disease progression by 37%, regardless of diabetes status (49).

Preventive strategies in kidney disease management

The landscape of kidney disease management is undergoing rapid transformation, driven by innovative therapeutic approaches, lifestyle interventions, and evolving research priorities. This evolution represents a convergence of multiple strategies aimed at improving patient outcomes, emphasizing the critical importance of prevention, early intervention, and comprehensive treatment (5). Significant advancements in therapeutic options are reshaping the field, with promising approaches such as cell therapy, regenerative medicine, and organoid technology under active investigation (50). Cell therapy, particularly the use of renal progenitor cells, offers the potential to replace damaged kidney tissue and reverse kidney damage rather than merely slowing its progression (51). Similarly, the development of kidney organoids, which compromise at least eleven different cell types and closely mimic human kidney tissue, represents a breakthrough in understanding kidney dysfunction and testing therapeutic interventions. These organoids hold promise for personalized treatment approaches and future implantation to enhance and repair renal function (52,53).

The complex nature of kidney disease necessitates a multi-targeted treatment strategy, combining various therapeutic agents with complementary mechanisms of action. Recent evidence supports the benefits of combination therapy, particularly for CKD associated with type 2 diabetes (54). Clinical trials are actively exploring the efficacy of such therapies, with promising results from studies involving SGLT2 inhibitors and other kidney-protective agents (55,56). This integrated approach addresses the multiple pathways and mechanisms involved in disease progression, aiming to achieve optimal outcomes by intervening at multiple levels (57).

Lifestyle interventions remain a cornerstone of kidney disease prevention and management. Comprehensive modifications, including dietary changes, physical activity, and risk factor management, play a crucial role in slowing disease progression (58). Specific recommendations include reducing sodium intake to less than 2,300 milligrams daily, limiting added sugars, and engaging in at least 30 minutes of physical activity most days of the week (59). These lifestyle adjustments not only support kidney health but also contribute to overall cardiovascular health and metabolic control, underscoring their importance in a holistic approach to kidney disease management (60).

Conclusion

The emergence of novel therapeutic classes has fundamentally transformed the treatment landscape for kidney disease. SGLT2 inhibitors, MRAs, and metabolic modulators represent distinct yet complementary approaches to addressing the complex pathophysiology of kidney disease. The robust clinical evidence supporting their efficacy, particularly for SGLT2 inhibitors, has established these agents as essential components of modern kidney disease management. As our understanding of disease mechanisms continues to evolve, the integration of these therapeutic classes offers promise for improving outcomes in patients with kidney disease, while ongoing research continues to refine their optimal use in clinical practice.

Conflicts of interest

The author declares that she has no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author utilized Perplexity to refine grammar points and language style in writing. Subsequently, the author thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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