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REVIEW ARTICLE

Exploring Novel Therapeutic Approaches for Chronic Kidney Disease

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Abstract: Chronic kidney disease (CKD) is a significant global health burden, affecting millions of individuals worldwide. Despite current treatment strategies focusing on glycemic control and renin-angiotensin system blockade, these approaches merely delay the progression to end-stage renal disease (ESRD) and are associated with potential adverse effects. Recent advancements in our understanding of the complex pathophysiology of CKD have unveiled various unique processes contributing to its development, including vascular alterations, podocyte and renal epithelial cell loss, matrix deposition, inflammation, and metabolic dysregulation. This comprehensive review critically evaluates novel therapeutic approaches targeting these distinct pathways implicated in CKD pathogenesis. Strategies discussed include endothelial glycocalyx restoration, endothelin receptor antagonists, anti-apoptotic and podocyte regeneration therapies, anti-inflammatory and antioxidant agents, sodium-glucose co-transporter 2 (SGLT2) inhibitors, mitochondria-targeted therapies, anti-fibrotic agents, and interventions targeting epithelial-to-mesenchymal transition (EMT). While preclinical studies have demonstrated promising results for many of these approaches, their translation to clinical settings has been challenging due to safety concerns, lack of efficacy in trials, and the heterogeneity of CKD pathogenesis. The review highlights the importance of identifying appropriate patient populations, developing precision medicine strategies, exploring combination therapies, and leveraging novel drug delivery systems and regenerative medicine approaches to overcome current obstacles and improve therapeutic outcomes for CKD patients.

Keywords: Chronic Kidney Disease; Renal Failure; Renin; Angiotensin; Aldosterone; Vascular disease.

1. Introduction

Chronic kidney disease (CKD) is a significant public health concern, affecting approximately 20 million Americans, with half a million individuals suffering from ESRD, the most severe form of the disease. The primary treatment options for ESRD are dialysis or kidney transplantation. However, the shortage of donor organs limits the accessibility of transplantation, while dialysis patients face an alarmingly high annual mortality rate of up to 20% [1, 2]. The leading causes of CKD and ESRD in the United States are diabetes mellitus (approximately 50% of cases) and hypertension (25% of cases), followed by polycystic kidney disease and glomerulonephritides [1, 3].

Notably, cardiovascular disease (CVD) remains the primary cause of death among individuals with CKD [4]. Despite significant progress in reducing the overall population's risk of CVD, this improvement has not translated to CKD patients, who exhibit a substantially higher mortality rate compared to non-CKD individuals, even when factors such as blood pressure, smoking status, and serum cholesterol levels are controlled [5, 6]. The accumulation of various toxins and metabolites in CKD patients may contribute to the development of "non-traditional risk factors," potentially increasing their mortality rate. CKD is typically diagnosed when the glomerular filtration rate (GFR) is less than 60 mL/min/1.73 m2 for more than three months [7]. Various stages of CKD have been established based on GFR levels, ranging from stage G1 (GFR >90 mL/min) to stage G5 (GFR <15 mL/min) [8, 9]. However, it is important to note that the staging system was primarily developed for research purposes, and a continuous decline in GFR represents an increased risk of mortality. Albuminuria, or the leakage of albumin or protein in the urine, is another functional abnormality that has gained prominence in the new classification guidelines [8, 9].

While decreased albuminuria is typically associated with protection against functional decline, its presence is substantially correlated with the development of ESRD, increased CVD risk, and mortality [10]. The two major histological and structural hallmarks of CKD are interstitial fibrosis and glomerular sclerosis [11], with glomerular alterations often being specific to the underlying etiology and useful for disease classification and diagnosis [12].

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2. Current therapeutic approaches

2.1. Angiotensin-Converting Enzyme Inhibitors (ACEIs] and Angiotensin Receptor Blockers (ARBs]

For over two decades, the cornerstones of CKD treatment have been ACEIs and ARBs (Figure 1] [13]. Preclinical studies demonstrated a reduction in intraglomerular hemodynamic pressure and proteinuria in rat models of kidney diseases, such as diabetic nephropathy and partial renal ablation, providing the initial rationale for investigating ACEi therapy [14, 15]. Clinical trials of ACEIs in patients with type 1 diabetes and nephropathy demonstrated improved renal outcomes compared to alternative methods of blood pressure reduction [16]. These findings established ACEIs as the standard of care for patients with diabetic nephropathy (DN). Subsequent research extended the reported benefit to individuals with late-stage renal disease and other causes of kidney disease [17, 18]. Similarly, ARBs also demonstrated beneficial effects in patients with type 2 diabetes and nephropathy [19, 20], further solidifying the renin-angiotensin pathway as a major therapeutic target for CKD. The potential of ACE/ARB therapy to lower intraglomerular filtration pressure has been well-documented [15]. Notably, the therapeutic efficacy of this treatment is closely linked to an early decline in estimated GFR [21], along with a reduction in proteinuria (or albuminuria) [22, 23]. While the incidence of renal failure has decreased since the introduction of ACEi and ARB treatment, the prevalence of CKD has continued to rise, with over 100,000 patients experiencing renal failure annually [1, 24]. Moreover, there has been no corresponding decline in diabetic ESRD [25] to match the remarkable reduction in cardiovascular events, stroke, and amputations observed in diabetes patients over the past two decades [26]. Unlike acute inflammatory glomerulonephritis, where immunosuppression can potentially reverse the condition, there are currently no medications capable of reversing the loss of renal function associated with CKD. However, ACEi or ARB therapy remains the gold standard for treating chronic proteinuric kidney disease, and any new treatment must demonstrate further benefit in conjunction with ACEi or ARB therapy. [5]

3. Novel approaches for regulating blood pressure and hemodynamics

3.1. Combination of ARB and ACEi

To achieve more comprehensive renin-angiotensin system (RAS) inhibition and potentially halt disease progression, researchers explored the combination of an ACE inhibitor and an ARB [27, 28]. The ONTARGET study evaluated the efficacy of the ACEi ramipril, the ARB telmisartan, or their combination in 25,920 patients with high-risk diabetes and/or vascular disease [29]. However, the study failed to establish a renoprotective advantage of combination ACEi/ARB therapy in proteinuric individuals, as the majority of participants recruited did not exhibit microalbuminuria or macroalbuminuria at baseline [29]. Furthermore, a substantial number of participants (784) permanently discontinued the randomized therapy due to hypotensive symptoms, primarily in the combination therapy group. Additionally, this group experienced a higher rate of participants reaching the primary renal outcome of dialysis, doubling of serum creatinine, or death compared to the monotherapy group, with acute renal failure being more common in patients with normotension.

3.2. Renal inhibition

An alternative strategy for RAS inhibition aims to prevent renin-mediated cleavage of angiotensinogen to angiotensin-1, the initial step in the renin-angiotensin-aldosterone cascade (Figure 1). The ALTITUDE trial evaluated the impact of the renin inhibitor aliskiren on renal outcomes in patients with diabetic nephropathy [31]. While adding aliskiren to either ACEi or ARB medication reduced albuminuria more than a placebo, it did not enhance the rate of eGFR loss or reduce renal events. Additionally, aliskiren was associated with an increased risk of hyperkalemia and stroke. Due to an increase in adverse events and a lack of benefit on the decline in renal function, the ALTITUDE study was terminated early. These results raise serious concerns about the safety of using total RAS inhibition as a treatment for progressive kidney disease [30].

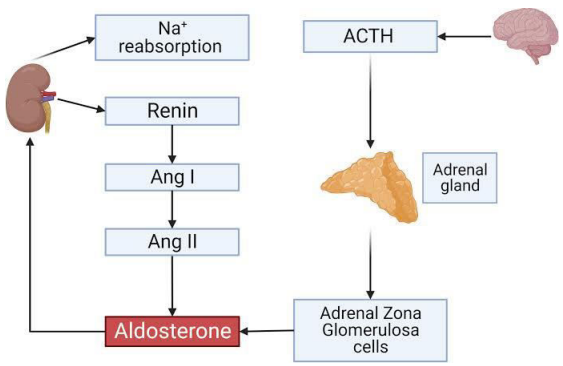

Figure 1. Renin angiotensin aldosterone system

3.3. Mineralocorticoid Receptor (MR) Antagonists

Despite the known risks of hyperkalemia associated with the MR antagonist spironolactone [36], trials investigating the efficacy of newer MR antagonists, such as finerenone (Bayer) [37], CS-3150 (Daiichi Sankyo), and MT-3995 (Mitsubishi Tanabe), are being conducted in combination with other treatments for diabetic nephropathy [38]. These studies aim to determine if appropriate dosing regimens can be found that provide both efficacy and prevent hyperkalemia. Strategies targeting pathways perpendicular to the RAAS appear to offer the benefit of non-overlapping safety profile issues.

3.4. Targeting the Vascular System

Kidney disease falls within the category of diabetic microvascular complications. Both clinical disease and experimental diabetes exhibit endothelial cell dysfunction, including proliferation and aberrant angiogenesis [39]. Retinal endothelial pathology similar to that observed in renal disease has been reported [40, 41], which may contribute to the high correlation between renal illness and retinopathy in diabetes. A characteristic of the early stages of experimental diabetes is an increase in glomerular size, which could result from podocyte hypertrophy, cellular endothelial hypertrophy, and hyperplasia (Figure 2) [42, 43]. Podocytes, which are a major source of VEGF, angiopoietins, and SDF, create a bidirectional signaling pathway with endothelial cells across the filtration barrier (Figure 2) [44]. This podocyte-endothelial cross-talk significantly mediates the development of albuminuria and the permselectivity of the filtration barrier [45].

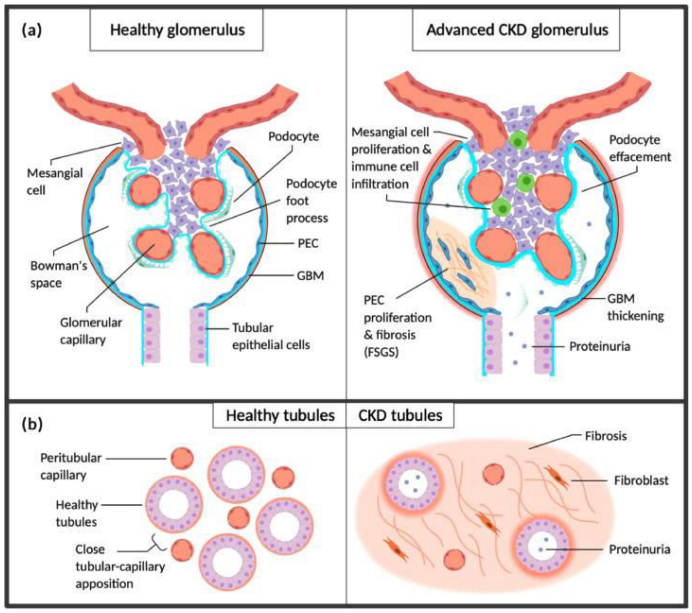

Figure 2. Treating CKD by focusing on the glomerulus

3.4.1. Endothelial Glycocalyx Restoration

The glycocalyx, a coat rich in glycoproteins and polysaccharides, covers mammalian cells (Figure 2] [46, 47]. The glomerular endothelial glycocalyx acts as a barrier, limiting the passage of plasma proteins through the filtration barrier and preventing proteinuria [46, 47]. One hypothesis suggests that the disruption and loss of the endothelial glycocalyx contribute to the onset of diabetes [48, 49]. Sulodexide, a highly purified mixture of glycosaminoglycans (80% fast-moving heparin and 20% dermatan sulfate), possesses anti-thrombotic, profibrinolytic properties, and the potential to prevent endothelial glycocalyx breakdown [50, 51]. However, in a multicenter, placebo-controlled, double-blind phase 3 study, sulodexide did not provide a significant benefit despite reducing urine albumin excretion in patients with type 2 diabetic nephropathy [52]. Although research is ongoing, alternative methods of restoring the endothelial glycocalyx, such as pharmacologic heparanase inhibition, have not yet been implemented in clinical settings [53].

3.4.2. Endothelin Receptor Antagonists

Preclinical studies of animal models of kidney disease have indicated that selective inhibition of the endothelin A (ETA) receptor, in combination with current treatments such as RAS interventions, is associated with renal protection [54]. Several potential mechanisms have been proposed to explain the renoprotective effects of ETA receptor blockade. It has been demonstrated that the ETA receptor antagonist atrasentan lowers albuminuria (Table 1) [55]. ETA receptor blockade also exerts vascular effects, resulting in glomerular vasodilation [56]. Additionally, ETA receptor blocking may reduce renal inflammation associated with endothelin, potentially by attenuating the inflammatory effects of albuminuria [57, 58].

Table 1. Active Phase II and Phase III clinical trials investigating novel therapeutic agents for renal disease

Drug	Mechanism of Action	Hypothesized Benefit	Trial Details	Notes
Atrasentan	ETA receptor antagonist	Renal protection	Phase III	Primary outcome measure: Time to composite of serum creatinine doubling or ESRD Enrollment: n = 4,148 Estimated Completion: July 2018
Canagliflozin	SGLT2 inhibitor	Renal protection	Phase III	Primary outcome measure: Time to composite of serum creatinine doubling, cardiovascular or renal death Enrollment: n = 3,700 Estimated Completion: January 2020
Pyridorin	Reducing advanced glycation end-product protein modification	Anti-fibrotic	Phase III	Primary outcome measure: Time to composite of serum creatinine rise ≥100% or ESRD Enrollment: n = 600 Estimated Completion: March 2018
ASP8232	NHE3 inhibitor	Anti-fibrotic	Phase II	Phase II trial in focal segmental glomerulosclerosis Enrollment data not available

3.5. Targeting Podocyte Injury and Loss

3.5.1. Anti-Apoptotic Therapy

Podocyte depletion is a critical event in the progression of glomerular disease, and strategies to prevent podocyte apoptosis have been actively investigated [59]. Preclinical studies have demonstrated the potential of various anti-apoptotic agents, such as caspase inhibitors, Bcl-2 agonists, and NF-ϰB inhibitors, in attenuating podocyte loss and proteinuria [60, 61]. However, the translation of these approaches to clinical settings has been challenging due to potential off-target effects and toxicity concerns

3.5.2. Podocyte Regeneration and Replacement Strategies

Given the limited capacity of podocytes for self-renewal, alternative strategies have focused on promoting podocyte regeneration or replacement. These include the use of stem cell-derived podocyte-like cells or the activation of resident progenitor cells within the glomerulus [62, 63]. While these approaches have shown promise in preclinical models, significant challenges remain, including the efficient delivery of cells to the glomerular compartment, ensuring proper integration and function, and addressing potential immune rejection issues

3.6. Targeting Inflammation and Oxidative Stress

3.6.1. Anti-Inflammatory Agents

Inflammation plays a crucial role in the pathogenesis of CKD, contributing to the progression of renal injury and fibrosis [64]. Various anti-inflammatory agents, such as corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and targeted therapies like anti-TNF-α agents, have been explored for their potential in CKD [65]. However, their clinical use is often limited by adverse effects, including increased risk of cardiovascular events and impaired renal function [66].

3.6.2. Antioxidant Therapies

Oxidative stress is a significant contributor to the development and progression of CKD [67]. Antioxidant therapies, such as vitamin E, N-acetylcysteine, and bardoxolone methyl, have been investigated as potential treatments for CKD [68, 69]. While some studies have shown promising results in reducing oxidative stress markers and improving renal function, others have reported adverse effects, including cardiovascular events and increased mortality [70]. The efficacy and safety of antioxidant therapies in CKD remain controversial, highlighting the need for further research.

3.7. Targeting Metabolic Dysregulation

3.7.1. SGLT2 Inhibitors

Sodium-glucose co-transporter 2 [SGLT2) inhibitors, initially developed for the treatment of type 2 diabetes, have demonstrated potential renoprotective effects in CKD patients [71]. These agents reduce glomerular hyperfiltration, lower intraglomerular pressure, and exert anti-inflammatory and antioxidant effects [72]. Several large clinical trials are currently underway to evaluate the efficacy of SGLT2 inhibitors in slowing the progression of CKD (Table 1).

3.7.2. Mitochondrial Targeted Therapies

Mitochondrial dysfunction has been implicated in the pathogenesis of CKD, contributing to oxidative stress, inflammation, and cell death [73]. Therapies targeting mitochondrial dysfunction, such as mitochondria-targeted antioxidants and mitochondrial biogenesis modulators, have shown promise in preclinical studies [74]. However, their translation to clinical settings has been limited, and further research is needed to evaluate their efficacy and safety.

3.8. Targeting Fibrosis

3.8.1. Anti-Fibrotic Agents

Renal fibrosis is a common pathway leading to the progressive loss of kidney function in CKD [75]. Various anti-fibrotic agents, including pirfenidone, nintedanib, and galectin-3 inhibitors, have been investigated for their potential in attenuating renal fibrosis [76, 77]. While some of these agents have shown promising results in preclinical studies and early clinical trials, their efficacy and safety in larger patient populations remain to be established.

3.8.2. Targeting Epithelial-to-Mesenchymal Transition (EMT)

Epithelial-to-mesenchymal transition (EMT) is a process that contributes to the development of renal fibrosis by promoting the generation of myofibroblasts [78]. Strategies targeting EMT, such as inhibitors of TGF-β signaling or epigenetic modulators, have been explored as potential anti-fibrotic therapies for CKD [79]. However, these approaches are still in the early stages of development, and their clinical translation remains a significant challenge.

3.9. Challenges in Clinical Development

3.9.1. Safety Concerns

Many novel therapeutic approaches for CKD have faced significant safety concerns, limiting their clinical development. These concerns can arise from off-target effects, toxicity, or exacerbation of existing comorbidities. Careful evaluation of safety profiles in preclinical studies and early clinical trials is crucial to identify and mitigate potential risks.

3.9.2. Lack of Efficacy in Clinical Trials

Despite promising preclinical data, several novel therapeutic agents have failed to demonstrate significant efficacy in clinical trials for CKD. This lack of efficacy can be attributed to various factors, including the heterogeneity of CKD pathogenesis, inadequate target engagement, and the use of suboptimal patient populations or endpoints.

3.9.3. Heterogeneity of CKD Pathogenesis

CKD is a complex disorder with multiple etiologies and pathogenic mechanisms, making it challenging to develop a single therapy that is effective for all patients. The heterogeneity of CKD pathogenesis highlights the need for personalized or targeted therapeutic approaches based on the underlying disease mechanisms and patient characteristics.

3.9.4. Identifying Appropriate Patient Populations

Selecting the appropriate patient population is crucial for the successful clinical development of novel CKD therapies. Identifying patients most likely to respond to a specific therapeutic approach and defining relevant inclusion criteria based on biomarkers or disease characteristics are essential for increasing the likelihood of observing significant treatment effects.

3.10. Future Perspectives

3.10.1. Precision Medicine Approach

The development of precision medicine approaches for CKD holds significant promise. By integrating genomic, proteomic, and metabolomic data with clinical and pathological information, it may be possible to identify specific molecular signatures or endotypes that can guide the selection of targeted therapies for individual patients [80].

3.10.2. Combination Therapies

Given the complexity of CKD pathogenesis, combination therapies targeting multiple pathways may be more effective than single-agent approaches. Rational combinations of agents with complementary mechanisms of action could potentially enhance efficacy while minimizing adverse effects [80].

3.10.3. Novel Drug Delivery Systems

Innovative drug delivery systems, such as nanoparticles, liposomes, or targeted delivery strategies, could improve the therapeutic index of existing and novel agents by enhancing their selectivity, bioavailability, and reducing off-target effects [80].

3.10.4. Regenerative Medicine Strategies

Regenerative medicine approaches, including stem cell-based therapies and tissue engineering strategies, hold promise for restoring renal function in CKD patients (80]. However, significant challenges remain, including the development of safe and effective cell sources, optimizing delivery methods, and addressing potential immune rejection issues.

4. Conclusion

In summary, this review provides a comprehensive overview of the current therapeutic landscape for chronic kidney disease and highlights several promising novel approaches targeting various pathways involved in the pathogenesis of CKD. While some of these strategies have shown potential in preclinical studies, their translation to clinical settings has been challenging, often due to safety concerns or lack of efficacy. Continued research efforts are crucial to identify safe and effective treatments that can slow or halt the progression of CKD, ultimately improving patient outcomes and reducing the burden of this debilitating disease.

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