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INVESTIGATING RENAL FUNCTION MODULATION IN CHRONIC KIDNEY DISEASE: INSIGHTS INTO PATHOPHYSIOLOGY AND THERAPEUTIC TARGETS

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ABSTRACT

Chronic kidney disease (CKD) is a progressive disorder characterized by persistent structural or functional renal abnormalities that impair filtration, tubular regulation, metabolic balance, and endocrine activity. Its increasing global burden is associated with aging, diabetes, hypertension, obesity, vascular disease, cardiovascular complications, and high healthcare costs. Renal function decline in CKD is not uniform; it reflects complex interactions among glomerular hemodynamic stress, tubular dysfunction, neurohormonal activation, oxidative injury, mitochondrial impairment, inflammation, vascular pathology, and fibrotic remodeling. Renal function modulation provides an integrated framework for understanding how residual nephron activity, albuminuria, renal blood flow, tubular transport, and structural remodeling influence disease progression. Key pathogenic mechanisms include glomerular hyperfiltration, podocyte injury, maladaptive tubular repair, renin–angiotensin–aldosterone system activation, immune-mediated injury, metabolic reprogramming, and renal fibrosis. Biomarkers such as estimated glomerular filtration rate, serum creatinine, cystatin C, albuminuria, tubular injury markers, inflammatory mediators, fibrosis markers, and omics-based signatures are increasingly important for risk prediction and therapeutic monitoring. Current and emerging interventions, including blood pressure control, RAAS blockade, sodium–glucose cotransporter 2 inhibitors, mineralocorticoid receptor antagonists, glucagon-like peptide-1 receptor agonists, anti-inflammatory agents, anti-fibrotic strategies, mitochondrial therapies, and precision nephrology approaches, may slow CKD progression. This review highlights pathophysiological mechanisms and therapeutic targets relevant to preserving renal function and delaying kidney failure.

KEYWORDS: Chronic kidney disease; Glomerular hyperfiltration; Renal fibrosis; Renal function modulation; Therapeutic targets

INTRODUCTION

Chronic kidney disease (CKD) is a progressive clinical disorder that is marked by persistent abnormalities in kidney structure or function that gradually lead to impaired ability of the kidney to maintain fluid, electrolyte, acid-base, endocrine, and metabolic homeostasis. It has become a significant community health issue due to its high prevalence, asymptomatic course, oftentimes late diagnosis, and a strong association with cardiovascular disease, hospitalization, disability, and premature mortality. The world burden of CKD is on the rise due to aging of the population, diabetes mellitus, high blood pressure, obesity, vascular disease, and improved survival in patients with acute and chronic diseases that predispose people to long-term kidney impairment [1,2]. CKD also presents a high socioeconomic burden in terms of costs of long-term monitoring, pharmacological therapy, dialysis, kidney transplantation, and management of cardiovascular complications [1,3].

The impairments of renal function in CKD are not a homogeneous or linear process. Patients can undergo slow or rapid deterioration or stepwise decline following acute injury or periods of seeming stability followed by accelerated loss of glomerular filtration rate (GFR). These various patterns of progression are an interaction of primary kidney disease, systemic comorbidities, residual nephron adaptation, hemodynamic stress, inflammatory activity, metabolic dysfunction, and therapeutic response [4,5]. Acute kidney injury could also play a critical transitional role to chronic renal impairment, especially when repair mechanisms become maladaptive and result in persistent tubular injury, interstitial inflammation, and fibrosis [6,7]. The mechanisms are important in understanding therapeutic windows of the nephron before it becomes irreversible due to nephron destruction.

The idea of renal functional modulation in CKD can be related to biological and therapeutic processes that can modify the rate of renal functional decline, residual nephron function, albuminuria, tubular transport, renal blood flow,

inflammatory signaling, and structural remodeling. In early CKD, compensatory hyperfiltration in the remaining nephrons may serve to maintain total GFR, but prolonged glomerular hyperfiltration raises intraglomerular pressure, contributes to podocyte damage, worsens albuminuria, and contributes to glomerulosclerosis [8,9]. This is further enhanced by hypertension, which enhances the experience of glomerular capillary stress and vascular damage and produces a cycle of nephron damage and adaptive overwork in the remaining functional units [10]. The proteinuria is thus not just a predictor of renal injury but is also an agent of tubular poisoning and inflammatory stimulation.

Another key factor that determines the development of CKD is tubulointerstitial injury. Tubular epithelial cells are highly active metabolically, very dependent on mitochondrial functioning, supply of oxygen, and intact transport systems. Prolonged tubular stress can result in cell-cycle arrest, senescence, release of inflammatory mediators, and maladaptive repair and is thus implicated in the connection between responses to acute injuries and chronic fibrosis [11,12]. The mitochondrial dysfunction and oxidative stress enhance renal injury due to the impairment of the fatty acid oxidation process, the increase in the reactive oxygen species, the damage to the cellular proteins and DNA, and the disruption of the tubular energy metabolism [13,14]. These mechanisms are in interaction with vascular rarefaction and tissue hypoxia, which further increase nephron loss.

Inflammation and fibrosis are the key ultimate pathways through which different CKD etiologies meet. Natural and adaptive immune responses also play a role in the production of cytokines, recruiting macrophages, activating complement, signaling inflammasomes, and sustained tissue damage [15,16]. Excess deposition of extracellular matrix, fibroblast activation, expansion of the myofibroblast, tubular atrophy, and loss of capillaries all occur as a result of fibrosis. Close interrelations exist between this fibrotic remodeling process and transforming growth factor-beta (TGF-beta), the activation of the renin–angiotensin–aldosterone system (RAAS), oxidative stress, and inflammatory mediators [17,18]. When an abundance of fibrosis has developed, kidney damage is less reversible, which makes an early intervention essential.

Therapeutic interventions of CKD are now more geared towards the regulation of these underlying pathways in lieu of merely treating late-stage complications. Anti-inflammatory or anti-fibrotic agents are targeted to mitigate hemodynamic stress, proteinuria, oxidative damage, inflammation, and fibrosis [19,20]. It is also being investigated to enhance risk prediction and tailored treatment through biomarkers and an improved signatures of tissue injury through biomarkers and improved signatures of tissue injury [21,22]. This review thus analyzes the modulation of renal functions in CKD through the integration of pathophysiological mechanisms, disease progression biomarkers, and disease therapeutic targets, which may help preserve renal function and improve clinical outcomes.

REVIEW

4.1 Conceptual Framework of Renal Function Modulation in CKD

Renal function modulation in chronic kidney disease (CKD) is the physiological, pathological, and therapeutic processes that determine residual kidney function, progression of the disease, and survival of the nephrons. The progression of CKD is not only determined by the initial cause of renal injury, but it also depends on adaptive and maladaptive responses involving glomerular hemodynamics, tubular function, renal blood flow, neurohormonal activation, inflammation, oxidative stress, mitochondrial dysfunction, and fibrotic remodeling [5,23]. Remaining nephrons in early stages, or during periods of compensation, enhance single-nephron filtration to maintain the overall glomerular filtration rate. Even though this adaptation can actually preserve renal function, long-term hyperfiltration elevates intraglomerular pressure, promotes podocyte stress, increases albumin leakage, and contributes to progressive glomerulosclerosis [8].

The tubular epithelial integrity also modulates renal function. Tubular cells control the management of electrolytes, acid-base, solute transport, and metabolic activity; thus, long-term tubular injury can hasten interstitial inflammation, capillary rarefaction, and fibrosis [11,24]. The subsequent deterioration of the mitochondrial functions, along with the oxidative stress, further worsens the tubular energy metabolism and predisposes the cells to a self-sustaining cycle of renal injury [13,14]. The renal functions are modulated by neurohormonal systems, namely, the renin-angiotensin-aldosterone system [25]. In this way, the renal activity restructuring is a comprehensive way of perceiving CKD as the dynamical disorder where the functional restructuring, cellular damage, and structural reorganization interrelate to define the long-term clinical outcomes.

4.2 Epidemiology and Clinical Burden of Chronic Kidney Disease

Chronic kidney disease (CKD) is a significant global health burden due to its rising prevalence, progressive disease course, and strong correlation with cardiovascular morbidity and premature mortality. The increasing trends in the number of people having diabetes mellitus, high blood pressure, obesity, aging, and vascular disease have provided significant contributions to the growth of CKD in the world [1,2]. CKD is often not diagnosed in the early stages of the disease, as renal functioning may deteriorate without any apparent symptoms. This later treatment results in continued nephron damage, albuminuria, vascular dysfunction, and metabolic complications to develop before therapeutic intervention is undertaken [4,5].

The clinical impact of CKD goes beyond the progressive decline in glomerular filtration rate. CKD patients experience a higher risk of anemia, mineral and bone disorders, metabolic acidosis, fluid overload, electrolyte imbalance, frailty, hospitalization, and a decrease in quality of life. One of the most severe complications of CKD is cardiovascular disease. CKD promotes hypertension, vascular calcification, endothelial dysfunction, left ventricular hypertrophy, heart failure, and atherosclerotic events [3,26]. There is an increased risk of mortality due to a reduction in kidney functional ability, especially in individuals with advanced CKD, albuminuria, diabetes, and cardiovascular comorbidities [27].

Another impact of CKD is that it poses a significant economic burden on health systems. High-level disease needs intensive care, multidisciplinary care, expensive drugs, dialysis, or transplantation of the kidneys. Dialysis dependence, in particular, is resource-demanding, is linked to high morbidity and limited daily functioning, and high healthcare utilization [1,2]. These epidemiological and clinical facts make it clear that there is a need to diagnose earlier, risk-stratify, and provide therapeutic interventions that do not impair renal functioning and delay the onset of kidney failure. Figure 1 shows the increasing incidence, late diagnosis, clinical complications, and economic burden as some of the factors that add to the global health burden of CKD.

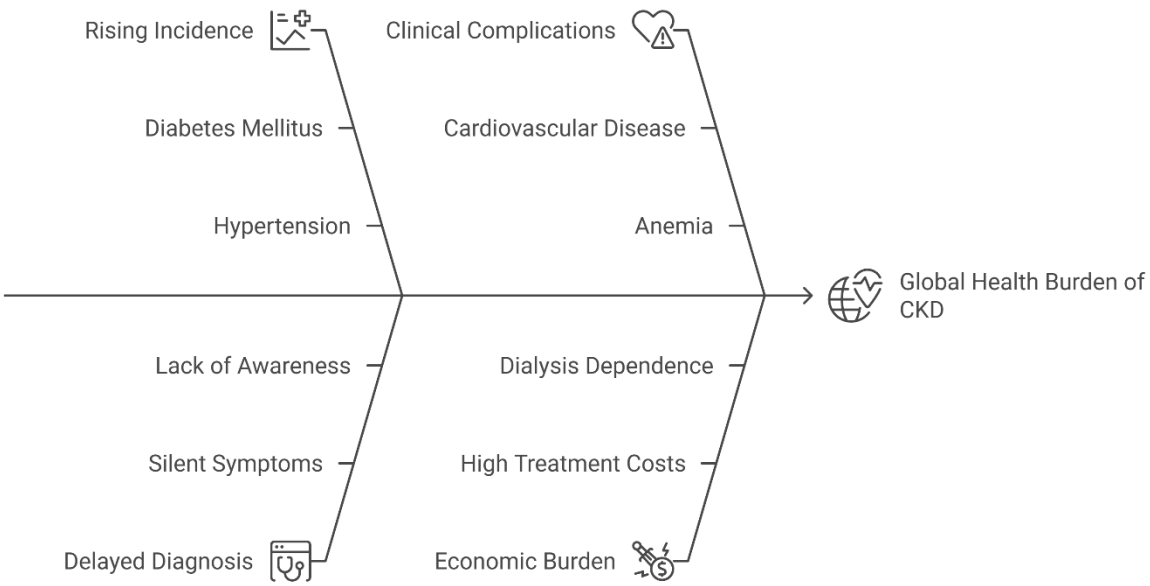

Figure 1. Understanding the Burden of Chronic Kidney Disease

4.3 Glomerular Hemodynamic Alterations and Hyperfiltration Injury

One of the key processes in the progression of chronic kidney disease (CKD) is the glomerular hemodynamic change. With the loss of nephrons, the surviving nephrons compensate by adapting to maintain equilibrium in the overall glomerular filtration rate. Such a response involves afferent arteriolar dilation, a rise in renal plasma flow, a rise in single-nephron filtration, and an increase in intraglomerular capillary pressure. Even though such adaptations could lead to a temporary preservation of the filtration capacity, chronic glomerular hyperfiltration predisposes the glomerular filtration barrier to mechanical damage and the onset of structural damage [8].

The podocytes are especially susceptible to injury caused by hyperfiltration due to a limited regenerative ability. Continuous intraglomerular hypertension stretches the podocytes, disrupts the integrity of the slit diaphragms, encourages podocyte detachment, and enhances leakage of albumin into the tubular lumen. Subsequently, albuminuria adds to the tubular inflammation, oxidative stress, and interstitial fibrosis, connecting the glomerular injury to the subsequent tubulointerstitial injury [9,10]. In the long term, stress on the capillary walls of the glomeruli facilitates expansion of the mesangial cells, deposition of extracellular matrix, sclerosis of the segments, and progressive atrophy of glomerular nephrons.

Glomerular hyperfiltration and intraglomerular pressure may be increased by systemic hypertension, diabetes, the consumption of high-protein diets, obesity, and the activation of the renin-angiotensin-aldosterone system. Especially important is the angiotensin II-mediated efferent arteriolar constriction, which maintains the high filtration pressure, as well as stimulates inflammation, oxidative stress, and fibrotic signaling [28]. Manipulation of glomerular hemodynamics in order to offer a significant nephroprotective approach is therefore a major 1. Inhibition of the renin-angiotensin system and sodium-glucose cotransporter 2 reduces intraglomerular pressure, decreases albuminuria, and slows down functional deterioration by restoring more favourable glomerular filtration dynamics [18,20]. Figure 2 demonstrates the compensatory glomerular adaptation, related risk factors, podocyte injury, tubulointerstitial damage, and therapeutic approaches to address the hemodynamic stress in CKD.

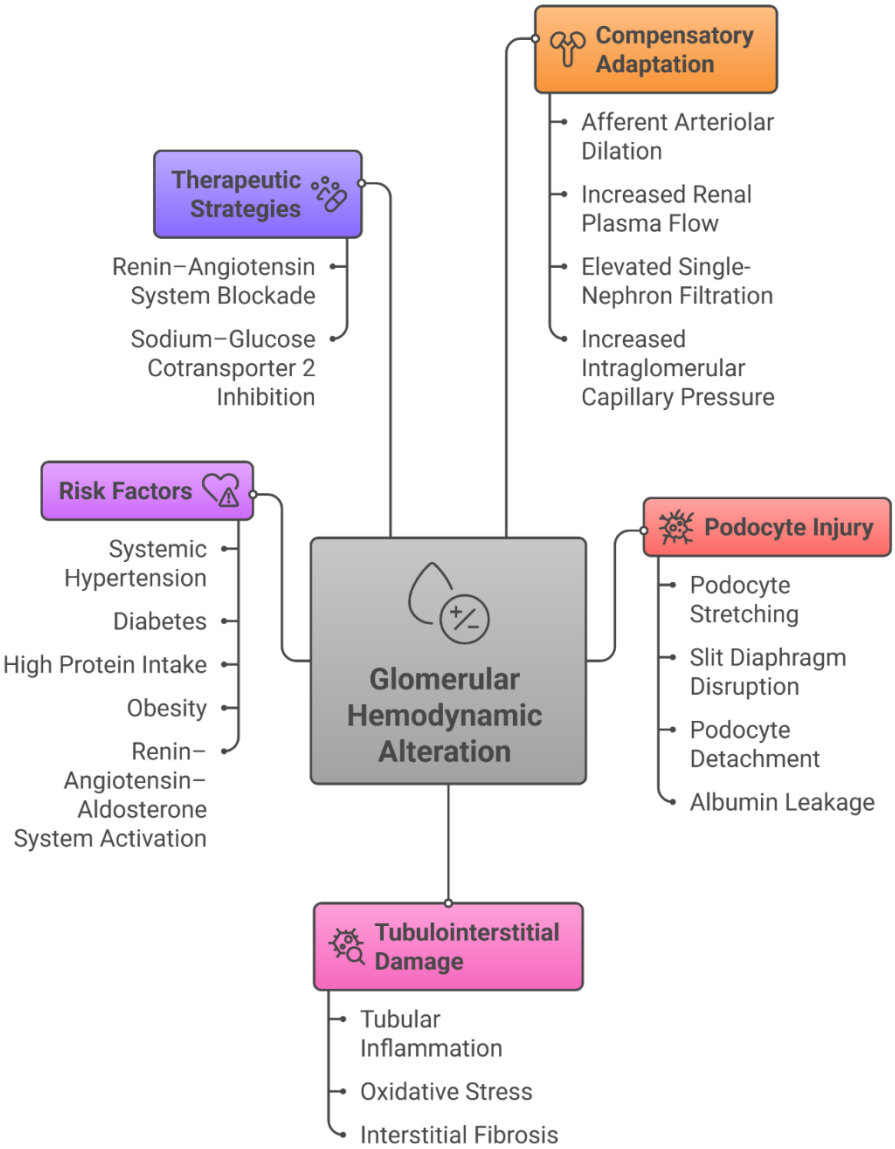

Figure 2. Glomerular Hemodynamic Alteration and Hyperfiltration Injury in CKD

4.4 Tubular Dysfunction and Maladaptive Repair Mechanisms

A significant cause of chronic kidney disease (CKD) progression is tubular dysfunction since the transporter cells (tubular epithelial cells) regulate the solute transport, electrolyte homeostasis, acid-base homeostasis, water handling, and renal metabolic activity. These are extremely energy-dependent cells, which are susceptible to hypoxia, protein overload, nephrotoxins, oxidative stress, mitochondrial injury, and inflammatory mediators. The progressive damage of tubules impairs reabsorptive and secretory functions, disturbs local metabolic control, and promotes interstitial inflammation and fibrosis [24].

Maladaptive repair is the response of injured cells of the tubular epithelial cell lining to incomplete normal regenerative recovery. Instead of repairing tissue integrity, injured tubular cells can be subjected to cell-cycle arrest, senescence, dedifferentiation, mitochondrial dysfunction, and secretion of profibrotic and proinflammatory mediators. These reactions trigger the recruitment of the macrophages, fibroblasts, pericytes, and endothelial cells, consequently, leading to the deposition of the extracellular matrix, the rarefaction of the capillaries, and the tubulointerstitial scarring [11,12]. It can be accelerated by acute kidney injury, especially when it is repeated or severe and shifts repair to adaptive regeneration and persistent epithelial stress and chronic remodelling [6,29].

The mechanism of connection between glomerular damage and interstitial disease is also associated with Tubular injury. Albumin and filtered protein may cause tubular oxidative stress, chemokine release, lysosomal dysfunction, and inflammatory cell recruitment and make the nephron injury worse than the glomerulus [5]. Mitochondrial dysfunction also inhibits fatty acid oxidation and ATP production, and thus limits the recovery of tubules and increases the risk of fibrosis development [30]. The targeted therapies related to mitochondrial homeostasis, inflammation, and maladaptive repair pathways may thus present valuable therapeutic opportunities in CKD to protect renal function.

4.6 Oxidative Stress, Mitochondrial Dysfunction, and Metabolic Reprogramming

Oxidative stress is a significant pathogenic process in chronic kidney disease (CKD), which is caused by the excessive generation of reactive oxygen species and the inability to eliminate the effects of these reactive oxygen species. Oxidative

stress is facilitated in CKD by uremic toxins, chronic inflammation, hyperglycemia, hypertension, endothelial dysfunction, mitochondrial injury, and activation of profibrotic signaling pathways. The overproduction of reactive oxygen species causes lipids, proteins, mitochondrial DNA, podocytes, tubular dysfunction, vascular impairment, and interstitial fibrosis [14,31].

Mitochondrial dysfunction is particularly significant in the tubular epithelial cells due to the fact that the cells require high levels of adenosine triphosphate to transport solutes, regulate electrolytes, maintain acid-base balance, and perform cellular repair. Lack of mitochondrial biogenesis, oxidative phosphorylation, altered mitochondrial dynamics, and reduced fatty acid oxidation impairment limit tubular energy availability and increase vulnerability to injury. All these abnormalities promote cell-cycle arrest, apoptosis, senescence, release of inflammatory mediators, and maladaptive repair, which promote progressive tubulointerstitial damage [13,30].

The additional connection between metabolic reprogramming and the development of CKD is the linking of mitochondrial dysfunction with the progression of CKD. Harvested renal cells can switch to glycolysis, decreasing energy efficiency and promoting a profibrotic phenotype. The mechanisms closely related to the altered glucose, lipid, and amino acid metabolism include fibroblast activation, accumulation of the extracellular matrix, and stress on the epithelium [17,18]. The therapeutic approaches to address the oxidative stress, mitochondrial preservation, fatty acid oxidation, and metabolic balance can therefore be used in modulating renal activity, decreasing fibrosis, and slowing the progression of CKD.

4.7 Inflammation and Immune-Mediated Renal Injury

The central role of inflammation in the progression of chronic kidney disease (CKD) and its interconnection with glomerular injury, tubular dysfunction, vascular pathology, oxidative stress, and fibrosis are interconnected. Chronic renal injury can trigger both innate and adaptive immune responses with the resultant release of cytokines, the production of chemokines, the recruitment of leukocytes, the activation of the complement, and long-term tissue remodelling. This inflammatory network involves tubular epithelial cells, podocytes, endothelial cells, macrophages, dendritic cells, lymphocytes, and fibroblasts, and CKD is a multicellular disease process rather than a pure hemodynamic disease process [15,16].

Renal injury mediated by the immune system develops through several interacting mechanisms. Injured renal cells result in the release of danger-associated molecular patterns that activate pattern-recognition receptors, nuclear factor-kappa B signaling, and inflammasome pathways. The activation of NLRP3 inflammasome facilitates the release of interleukin-18 and interleukin-1β, and enhances the release of endothelial cell dysfunction, oxidative stress, and tubular damage [32,33]. The infiltration of macrophages is specifically relevant since the macrophages may enhance injury based on local stimuli or repair and fibrosis based on local stimuli.

Fibrotic remodelling is also facilitated by chronic inflammation. The activation of the immune system also leads to permanent structural damage by stimulating the activation of fibroblasts, the proliferation and differentiation of myofibroblasts, the deposition of the extracellular matrix, and the rarefaction of the capillary bed [17,18]. This association justifies the growing research on the use of anti-inflammatory strategies as a treatment option in CKD. Targeting of cytokine signaling, chemokine pathways, complement activation, inflammasome activity, and immune–stromal interactions may offer potential to mitigate renal injury, preserve residual nephron function, and delay renal failure.

4.8 Renal Fibrosis as a Final Common Pathway

Renal fibrosis is generally considered an end-stage pathway of a progressive kidney disease (CKD) in that a wide range of renal insults eventually lead to excessive accumulation of the extracellular matrix, tubular atrophy, tubular capillary rarefaction, glomerulosclerosis, and ultimately, irreversible loss of nephrons. Fibrosis is a maladaptive wound-healing response in which persistent injury triggers a wound-healing response, involving the activation of fibroblasts, pericytes, inflammatory cells, tubular epithelial cells, and endothelial cells. This process occurs gradually as functional renal parenchyma is replaced by scar tissue, decreasing glomerular filtration capacity, and impairing tubular function [17,18].

One of the most crucial profibrotic mediators in CKD is the transformation of growth factor-beta (TGF-B). It stimulates fibroblast activity, differentiation of the myofibroblasts, collagen synthesis, deposition of the extracellular matrix, and inhibition of matrix degradation. TGF-b signaling is also interactive with oxidative stress, activation of the renin - angiotensin-aldosterone system, inflammation, and metabolic dysfunction, and is self-perpetuating as a fibrotic environment [33,34]. Fibrotic remodelling and nephron damage are further intensified by additional pathways, such as Wnt/ -catenin, Notch, and connective tissue growth factor, endothelin signalling, and hypoxia-inducible pathways [20,35]. Long-term renal outcome has been observed to be most predicted by tubulointerstitial fibrosis since it impairs oxygen delivery, tubular transport, peritubular capillary integrity, and epithelial repair capacity. When the fibrosis is widespread, damage to the kidney can hardly be reversed, so it is necessary to detect fibrosis early and provide timely therapeutic intervention [24]. Anti-fibrotic approaches to TGF-b-related signalling, fibroblast activation, inflammatory, oxidative stress, and metabolic reprogramming may thus offer valuable opportunities in preserving of renal functions in CKD. Table 1 reveals important processes that contribute to CKD progression.

Table 1. Major Pathophysiological Mechanisms Involved in CKD Progression

Mechanism	Pathophysiological role in CKD	Functional consequence	Reference
Glomerular hyperfiltration	Increases single-nephron filtration and intraglomerular pressure after nephron loss	Podocyte injury, albuminuria, and glomerulosclerosis	[19]

Hypertensive renal injury	Produces vascular stress, glomerular pressure overload, and endothelial dysfunction	Accelerated decline in renal function	[20]
Tubular maladaptive repair	Prevents complete epithelial recovery after injury and promotes chronic remodeling	Tubulointerstitial inflammation and fibrosis	[25]
RAAS activation	Enhances angiotensin II and aldosterone signaling	Proteinuria, sodium retention, hypertension, and fibrosis	[27]
Oxidative stress	Increases reactive oxygen species and cellular damage	Tubular dysfunction, endothelial injury, and fibrosis	[31]
Mitochondrial dysfunction	Impairs oxidative phosphorylation and tubular energy production	Reduced tubular repair capacity and progressive nephron injury	[33]
Immune-mediated renal injury	Activates cytokines, chemokines, inflammasomes, and immune-cell infiltration	Persistent inflammation and tissue remodeling	[36]
Renal fibrosis	Promotes extracellular matrix deposition and replacement of functional tissue	Irreversible nephron loss and kidney failure progression	[5]

4.9 Biomarkers for Renal Function Modulation and Disease Progression

Biomarkers have a critical role in assessing the change in renal functioning, recognizing patients at high risk of developing chronic kidney disease (CKD), and during therapeutic response monitoring. The traditional biomarkers like serum creatinine, estimated glomerular filtration rate (eGFR), and urine albumin-to-creatinine ratio are still at the center of clinical assessment. eGFR gives an approximation of the filtration capacity, and albuminuria is an indicator of dysfunction of glomerular barriers and is closely related to progressive nephron injury and cardiovascular risk [21,22]. As it is widely used, serum creatinine is affected by age, sex, muscle mass, diet, and hydration status, which limits its sensitivity in the early detection of renal impairment. Cystatin C could be useful in enhancing risk prediction as it is less related to muscle mass and can help to refine the estimation of kidney functionality in the selected patients [21].

The new biomarkers can help to provide more information on the presence of tubular injury, inflammation, fibrosis, and metabolic dysfunction. The molecules and proteins that have been studied as a marker of active renal injury and accelerated decline include kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, monocyte chemoattractant protein-1, tumor necrosis factor receptors, collagen fragments, and inflammatory cytokines [36,37]. These indicators can contribute to the identification of subclinical damage before significant losses of eGFR.

Multiplexing of phenotypes of CKD and predicting progression with greater accuracy are being made possible by multi-omics, such as proteomics, metabolomics, transcriptomics, and urinary peptide profiling [22]. Strategies based on biomarkers could be used to support personalized therapy by targeting the different hemodynamic, inflammatory, fibrotic, and metabolic drivers of renal decline. Nevertheless, most of the new biomarkers are yet to be validated, standardized, cost-effectiveness studies, and integrated into routine clinical practice before they find application in CKD management. Table 2 represents the key biomarkers to monitor CKD progression.

Table 2. Biomarkers for Renal Function Modulation and CKD Progression

Biomarker category	**Representative biomarkers**	**Clinical relevance**	**Reference**
Filtration biomarkers	Serum creatinine and estimated glomerular filtration rate	Assess renal filtration capacity and CKD staging	[40]
Alternative filtration marker	Cystatin C	Improves kidney function estimation in selected patients	[6]
Glomerular injury marker	Albuminuria	Indicates glomerular barrier injury and predicts progression risk	[4]
Tubular injury markers	Kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin	Detect tubular epithelial injury before major filtration decline	[39]
Inflammatory biomarkers	Cytokines and tumor necrosis factor-related markers	Reflect immune activation and inflammatory renal injury	[40]
Fibrosis-related biomarkers	Collagen fragments and profibrotic mediators	Indicate extracellular matrix remodeling and scarring activity	[45]
Multi-omics biomarkers	Proteomic, metabolomic, and transcriptomic signatures	Support risk prediction and precision nephrology	[45]

4.10 Therapeutic Targets and Emerging Interventions for CKD Management

The therapeutic goal of chronic kidney disease (CKD) is to slow the loss of renal function by altering the hemodynamic stress, proteinuria, inflammation, oxidative damage, metabolic impairment, and fibrosis. Still, fundamental interventions, especially in proteinuric CKD, are angiotensin-converting enzyme inhibitors and angiotensin receptor blockers that lower intraglomerular pressure, albuminuria, and angiotensin II-mediated fibrotic signaling [18,25]. The antagonist of

mineralocorticoid receptor also has additional therapeutic value since they inhibit inflammation and fibrosis caused by aldosterone, although hyperkalemia risk is also a risk factor that requires close clinical attention [38].
The sodium-glucose cotransporter 2 (SGLT2) inhibitors have become valuable nephroprotective agents due to their ability to restore tubuloglomerular feedback, reduce glomerular hyperfiltration, lower the albuminuria, and provide cardiovascular benefits. They not only control glycemic levels but also modulate renal oxygen demand, the metabolic stress, inflammation, and fibrosis [20,39]. Agonists of glucagon-like peptide-1 receptors can also facilitate the management of CKD, particularly in patients with diabetes, obesity, and the risk of cardiovascular diseases, through the enhancement of glycemic control, reduction of weight, anti-inflammatory, and possibly the reduction of albuminuria [39].
New interventions are becoming more focused on the molecular and cellular processes of CKD progression. Cytokine, chemokine, complement activation, and inflammasome signaling anti-inflammatory therapies are being investigated [15,32]. Transforming growth factor-beta, Wnt/ beta-catenin, growth factors, endothelin signaling, fibroblast activation, and remodeling of the extracellular matrix may be anti-fibrotic strategies to help limit irreversible scarring [19,40]. The future of renal function modulation of CKD is the use of mitochondrial protective agents, metabolic modulators, regenerative therapies, and biomarker-based precision therapies. Table 3 demonstrates the therapeutic goals applicable in CKD to modify the renal functions.

Table 3. Therapeutic Targets and Emerging Interventions for Renal Function Modulation in CKD

Therapeutic target or intervention	Primary mechanism	Expected renal benefit	Reference
Blood pressure control	Reduces systemic and intraglomerular pressure	Slows nephron injury and renal function decline	[20]
RAAS blockade	Inhibits angiotensin II-mediated efferent arteriolar constriction and fibrosis	Reduces albuminuria and glomerular hypertension	[18]
Mineralocorticoid receptor antagonists	Limits aldosterone-mediated inflammation and fibrosis	Improves cardiorenal protection in selected CKD patients	[28]
SGLT2 inhibitors	Restore tubuloglomerular feedback and reduce hyperfiltration	Lower albuminuria and slow CKD progression	[32]
Anti-inflammatory therapy	Targets cytokines, chemokines, complement, and inflammasome signaling	Reduces immune-mediated renal injury	[36]
Anti-fibrotic therapy	Modulates TGF-β, Wnt/β-catenin, growth factors, and fibroblast activation	Limits extracellular matrix accumulation and renal scarring	[33]
Mitochondrial and metabolic therapies	Preserve tubular energy metabolism and reduce oxidative injury	Improve tubular resilience and repair capacity	[33]
Precision nephrology	Integrates biomarkers, omics, and individualized risk prediction	Enables mechanism-based treatment selection	[4]

Limitations and Future Directions
The heterogeneity of chronic kidney disease (CKD) is the limitation of this review, as disease mechanisms differ between diabetic kidney disease, hypertensive nephropathy, glomerulonephritis, polycystic kidney disease, and post-acute kidney injury states. Most of the therapeutic targets addressed are either experimental or early-phase clinical targets and not large-scale outcome trials. Tubular injury, inflammatory, fibrosis, and metabolic dysfunction biomarkers are inadequately standardized to be utilized in clinical practice. Other factors affecting CKD progression include age, comorbidities, socioeconomic factors, medication adherence, and access to specialized care, which might restrict generalizability to different populations.
Future CKD studies need to focus more on precision nephrology techniques, which can combine clinical parameters, genomics, proteomics, metabolomics, imaging, and validated biomarkers to determine which disease mechanisms are dominant in individual patients. Further longitudinal studies are required to better understand the effects of newly developed therapies that target inflammation, fibrosis, oxidative stress, mitochondrial dysfunction, and metabolic reprogramming on hard renal outcomes. Individualized combination therapy, earlier intervention, risk prediction based on artificial intelligence, and improved monitoring based on biomarkers may improve the preservation of renal function and delay the progression to kidney failure.

CONCLUSION
It is concluded in this review that chronic kidney disease is a progressive, multifactorial disorder in which a decline in renal function is the result of interaction between hemodynamic stress and tubular dysfunction, neurohormonal activation, oxidative damage, mitochondrial impairment, inflammation, vascular damage, and fibrosis. Renal function modulation is a beneficial model to comprehend how these processes affect residual nephron functioning, albuminuria, glomerular filtration, tubular integrity, and disease progression. Major contributors to irreversible nephron loss include glomerular hyperfiltration, activation of the renin-angiotensin-aldosterone system, maladaptive tubular repair, immune-mediated injury, and accumulation of extracellular matrix. The existence of current therapeutic approaches, such as blood pressure

control, RAAS blockade, sodium-glucose cotransporter 2, mineralocortin receptor, and cardiometabolic risk approaches, indicates that guiding the CKD progression through targeting key pathogenic pathways can help slow the CKD progression and improve clinical outcomes. Anti-inflammatory, anti-fibrotic, mitochondrial, metabolic, regenerative, and biomarker-directed strategies can also be expanded into the therapeutic range. Further development will be based on prior diagnosis, confirmed biomarkers, customized risk estimation, and treatment combinations that are customized. In general, to prevent kidney failure and slow cardiovascular and systemic complications, renal functional disturbances and structural remodeling must be integrated in the preservation of renal function in CKD.

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