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Nephron Loss And Systemic Risk: An Overview Of Chronic Kidney Disease

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Abstract

Persistent abnormalities in urine, abnormalities in structure, or reduced excretory renal function suggestive of a loss of functional nephrons are the hallmarks of chronic kidney disease. The mainstays of therapy are blood pressure regulation, renin-angiotensin system inhibition, and disease-specific therapies. Diagnosis and therapy are necessary for CKD consequences that impact cardiovascular health and quality of life, such as anemia, metabolic acidosis, and secondary hyperparathyroidism. GFR, which can be approximated using equations or evaluated using exogenous markers like DTPA and iohexol, is the best biomarker of total renal function currently available. A higher chance of CKD development and death is linked to the presence of proteinuria. Renal biopsy specimens can provide conclusive proof of chronic kidney disease by exhibiting typical modifications such interstitial fibrosis, tubular atrophy, and glomerular sclerosis. Among the complications include iron insufficiency, decreased red blood cell survival, and anemia brought on by the kidney's decreased production of erythropoietin. Mineral bone disease is brought on by abnormalities in the metabolism of calcium, phosphate, and vitamin D. Individuals with chronic kidney disease (CKD) have a five to ten times higher risk of dying before reaching the terminal stages of the disease.

1. Introduction

Chronic kidney disease (CKD) is a progressive and irreversible disorder characterized by structural or functional impairment of the kidneys over a prolonged period. It develops gradually and often remains asymptomatic during its early stages;

however, as the disease advances, patients may experience fatigue, nausea, edema, hypertension, and cognitive disturbances [1]. CKD is associated with several complications, including anemia, bone disorders, electrolyte imbalance, and cardiovascular disease, all of which contribute significantly to morbidity and mortality. The condition is commonly caused by diabetes mellitus, hypertension, glomerulonephritis, and polycystic kidney disease, while family history and aging also increase susceptibility [2]. Diagnosis primarily depends on the estimation of glomerular filtration rate (GFR) and detection of albuminuria through urine analysis. Imaging techniques and kidney biopsy may also be employed to determine the underlying cause and severity of the disease [3].

According to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, CKD is classified into stages G1 to G5 on the basis of GFR, while albuminuria categories A1–A3 further assess disease severity. A persistent GFR below 60 ml/min/1.73 m^2 for more than three months is considered diagnostic of CKD [4]. Globally, CKD represents a major public health challenge, affecting hundreds of millions of people and ranking among the leading causes of death worldwide. The increasing prevalence of diabetes, hypertension, and aging populations has further amplified the burden of CKD, and it is predicted to become one of the top causes of mortality by 2040 [5].

CKD results in progressive deterioration of kidney function, eventually leading to end-stage renal disease (ESRD), where dialysis or kidney transplantation becomes necessary for survival [6]. Disturbances in mineral metabolism are common in advanced disease, particularly abnormalities in phosphate and calcium balance. Consequently, phosphate binders are widely used in CKD management to prevent bone disease and secondary hyperparathyroidism [7]. Earlier aluminum-based phosphate binders were highly effective but later proved toxic due to their association with neurological and bone disorders. Calcium-based binders subsequently became popular; however, concerns regarding calcium overload encouraged the development of newer aluminum- and calcium-free alternatives such as magnesium- and lanthanum-based binders [8].

Patho physiologically, CKD is characterized by glomerulosclerosis, interstitial fibrosis, inflammation, and progressive nephron loss. Persistent injury to renal tissues stimulates fibrosis through activation of epithelial cells and myofibroblasts, accompanied by inflammatory cytokine release [9]. Hemodynamic changes within the kidneys, especially glomerular hyperfiltration caused by hypertension, further accelerate renal damage. Therapeutic strategies therefore focus on slowing disease progression by controlling blood pressure, blood glucose, and albuminuria [10]. Angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) remain the cornerstone of CKD therapy because they reduce glomerular pressure and proteinuria [11]. Lifestyle modifications, including dietary salt restriction, physical activity, and avoidance of nephrotoxic drugs such as NSAIDs, are also essential components of management [12].

Despite advances in dialysis and renal replacement therapy, CKD continues to impose a substantial economic and healthcare burden worldwide. Access to renal replacement therapy remains limited in many developing countries, contributing to premature mortality [13]. Therefore, early detection, prevention, and development of novel therapeutic approaches are essential to reduce the global impact of chronic kidney disease.

ETIOLOGY AND RISK FACTOR

Causes of Chronic Kidney Disease

Chronic kidney disease (CKD) develops from multiple underlying conditions that progressively impair kidney structure and function. Major causes include hypertension, diabetes mellitus, glomerulonephritis, chronic tubulointerstitial nephritis, genetic or cystic kidney disorders, and vascular diseases [14]. Other less common

causes include sickle cell nephropathy, vasculitis, plasma cell disorders, malignancies, and obstructive pathologies. CKD may arise from three principal categories of disorders: prerenal, intrinsic renal, and postrenal diseases [15].

Prerenal disease results from prolonged reduction in renal blood flow, commonly associated with chronic heart failure or liver cirrhosis [16]. Persistent hypoperfusion may eventually lead to ischemic injury and progressive nephron loss. Intrinsic renal diseases involve direct damage to kidney tissues and vasculature [17]. Nephrosclerosis, renal artery stenosis, fibromuscular dysplasia, glomerulosclerosis, and tubulointerstitial fibrosis are important intrinsic causes that gradually impair filtration capacity. Postrenal causes occur due to chronic urinary obstruction resulting from kidney stones, tumors, prostatic enlargement, congenital abnormalities, neurogenic bladder, or retroperitoneal fibrosis. Long-standing obstruction ultimately damages renal tissues and contributes to CKD progression [18].

Risk Factors of Chronic Kidney Disease

Risk factors for CKD are classified into non-modifiable and modifiable factors. Non-modifiable factors include advanced age, male gender, family history, ethnicity, and genetic predisposition. Genetic polymorphisms involving the renin-angiotensin-aldosterone system (RAAS) and genes associated with renal fibrosis have been linked with increased susceptibility to CKD and diabetic nephropathy [19].

Modifiable risk factors include hypertension, diabetes mellitus, obesity, smoking, metabolic syndrome, dyslipidemia, insulin resistance, and proteinuria. Elevated systolic blood pressure, particularly nocturnal hypertension, strongly predicts CKD progression and cardiovascular complications [20]. Persistent proteinuria significantly accelerates kidney damage by promoting glomerular injury and fibrosis. Lifestyle-related factors such as physical inactivity, poor dietary habits, and exposure to nephrotoxic substances further worsen disease progression. Early management of blood pressure, blood glucose, and proteinuria can substantially slow the decline in renal function [21].

Social and Environmental Factor

Social and environmental determinants also contribute significantly to the onset and progression of CKD. Obesity, smoking, poor nutrition, and sedentary lifestyle are closely associated with worsening renal impairment [22]. Environmental exposure to heavy metals, industrial chemicals, and certain medications increases the risk of kidney injury, especially in developing countries. In some regions, infections such as HIV and exposure to agricultural toxins are major contributors to CKD prevalence [23].

Activation of the renin-angiotensin-aldosterone system plays an important role in hypertension, proteinuria, and renal fibrosis. Studies have shown that reducing severe proteinuria through dietary interventions and RAAS inhibition improves renal outcomes. Metabolic abnormalities including hyperuricemia and abnormal lipid metabolism further accelerate nephron damage and increase cardiovascular risk [24]. Because CKD is strongly influenced by socioeconomic, environmental, and lifestyle factors, preventive strategies emphasizing public awareness, healthy lifestyle modification, and early screening are essential for reducing the global burden of chronic kidney disease (Figure 1).

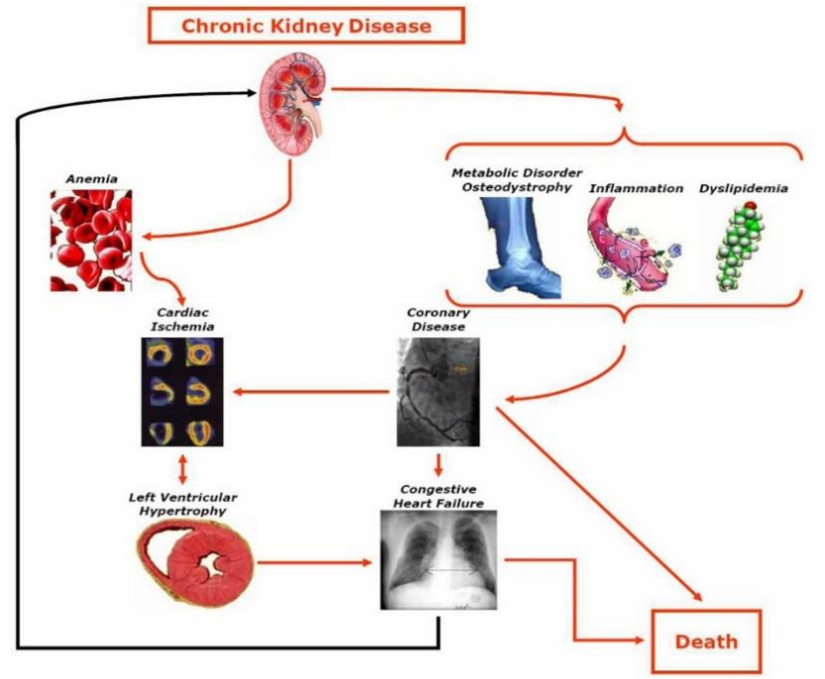

Figure 1. Chronic renal illness can trigger a series of events that eventually result in cardiovascular disease and, in certain situations, death, as seen in Figure 1. The black arrow depicts a feedback loop in which kidney illness is exacerbated by heart failure, while the red arrows show the disease-causing pathways.

Clinical Presentation: Usually, regular screenings, blood chemical profiles, or urine tests are used to identify chronic kidney disease. It could be unintentionally found in certain situations. Less often occurring symptoms include nocturia (frequent midnight urination), hematuria (severe blood in the urine), "foamy urine," which may be a sign of albuminuria (protein in the urine), and decreased urine flow. Patients may experience shortness of breath, pruritus (itchiness), confusion, exhaustion, appetite loss, nausea, vomiting, a metallic taste, and inadvertent weight loss when their chronic kidney disease worsens. Conditions such as obstructive uropathy, kidney stones, kidney infection (pyelonephritis), or polycystic kidney disease should be taken into consideration if flank pain or enlarged kidneys are present [25].

Future Directions of Chronic Kidney Disease:

Any long-term imbalance in kidney function or structure that has health repercussions and lasts for at least three months, regardless of the underlying cause, is considered chronic kidney disease, according to current international recommendations [26]. People are still at a high risk of developing end-stage renal disease (ESRD) or dying from any reason, even with advancements in treatment that can partially restore kidney function [27].

According to recent research, the best strategies to decrease the progression of chronic kidney disease include treating glomerular hyperfiltration, managing metabolic disorders, and reducing risk factors that lead to kidney damage, such as diabetes, hypertension, high cholesterol, obesity, and smoking [28].

Reversing chronic oxygen deprivation in kidney tissues, lowering inflammation, lowering iron accumulation, blocking the kidneys' plasminogen activator inhibitor (PAI-1) [29] and acting as antifibrotic agents by blocking growth factors like transforming growth factor beta (TGF-β) [30], which are implicated in various types of chronic kidney disease, are some of the ways that medications that block the renin-angiotensin system also aid in reducing kidney damage [31].

Advances in Early Detection:

(RAAS) is further disrupted by mineralocorticoid receptor antagonists (MRAs), which limit the effects of aldosterone and help reduce fibrosis in a number of organs,

including the heart, kidneys, and blood vessels [32]. Since they appear to have fewer adverse effects, such as elevated potassium levels (hyperkalemia), newer nonsteroidal MRAs, such as finerenone, may be especially helpful for individuals with chronic kidney disease [33].

Biomarkers of Early Detection: Studies on rats that are sleep deprived have shown that the telencephalon's dendrites contain the proline-rich protein dendrin. Dendrin is expressed not just in the brain but also in the kidneys, particularly in the loops of glomerular capillaries and podocytes. This protein is a crucial component of the slit diaphragm complex, controls podocyte activity, and aids in glomerular filtration. The movement of dendrin from the cell membrane to the nucleus promotes apoptosis (programmed cell death) when the kidneys are damaged and TGF-β levels increase [34]. Dendrin functions in the nucleus as a transcription factor for the cytosolic enzyme cathepsin L, which increases apoptosis sensitivity in response to TGF-β. Dendrin's nuclear migration could act as indicator of renal disorders [35].

Another significant protein that is essential in the formation and maintenance of the glomerular filtration barrier is nephrin, a transmembrane protein present in glomerular podocytes. It can be found on the podocyte foot processes' lateral surfaces. The main function of nephrin is to stop proteins from passing through the glomerular barrier. Children with Finnish type congenital nephrotic syndrome were the first to be observed to be affected [36]. Damage to podocytes first manifests as alterations to the slit diaphragm, foot process structural remodeling that results in filtration slit fusion, and dissociation from the glomerular basement membrane [37].

Genetic testing and Precise Medicine

Next Generation Sequencing to identify Genes in kidney disease: Currently, three next-generation sequencing (NGS) methods are being utilized to enhance the detection of hereditary diseases such as chronic kidney disease: whole exome sequencing, whole genome sequencing, and targeted panel sequencing. Numerous research investigating the role of individual genes in renal disease have been conducted since the introduction of NGS. As a result, hundreds of genes that could contribute to the onset and course of chronic kidney disease have been found. Our knowledge of particular genes and the disease pathways linked to chronic kidney disease has greatly benefited from each of these NGS techniques (Figure 2).

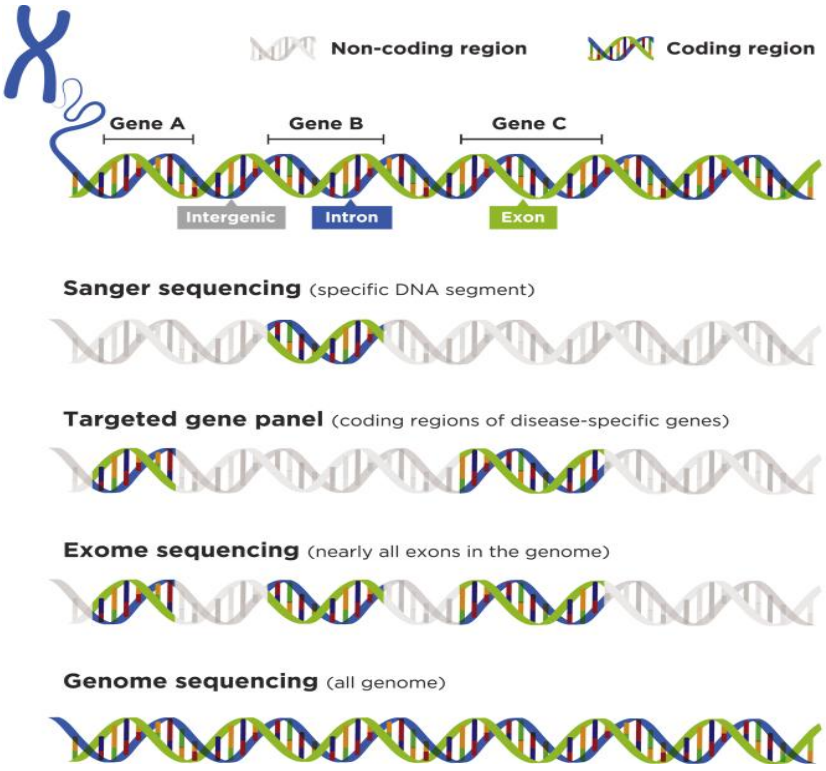

Figure 2: Genetic testing can be done in a number of ways, each with a specific use. Only a small section of the genome is the focus of Sanger sequencing. A specified set of genes' coding regions are the focus of targeted gene panels. Whole genome sequencing, on the other hand, covers practically the whole genome, whereas whole exome sequencing captures almost all of the genome's coding sequences.

NOVEL THERAPEUTIC STRATEGIES

Precision Medicine

Precision medicine has emerged as a promising approach in the management of chronic kidney disease (CKD), particularly in patients with hyperkalemia, a common electrolyte imbalance in advanced renal disease. Renin-angiotensin-aldosterone system (RAAS) inhibitors are widely used to reduce proteinuria and slow CKD progression; however, these agents frequently increase potassium levels, limiting their long-term use [38]. Recently developed potassium binders, including patrioteer and sodium zirconium cyclosilicate, have demonstrated effectiveness in controlling hyperkalemia while allowing continuation of RAAS blockade. Additional therapies such as sodium-based alkali and mineralocorticoid receptor antagonists may further preserve kidney function and delay disease progression [39].

The Gut Kidney Axis

The "Gut-Kidney Axis" describes the interaction between intestinal microbiota and kidney function in CKD. Alterations in gut microbiota contribute to inflammation, toxin accumulation, and progression of renal dysfunction. Consequently, therapies targeting gut dysbiosis have gained considerable attention. Emerging approaches include probiotics, dietary interventions, genetically engineered "smart bacteria," and fecal microbiota transplantation (FMT). Furthermore, alkaline phosphatase (ALP) has been identified as an important therapeutic target because of its involvement in inflammation, vascular calcification, oxidative stress, and kidney-related bone disorders. Epigenetic therapies such as microRNA-based treatment and bromodomain inhibitors like Apabetalone have shown potential in improving renal outcomes and reducing CKD-associated complications [40].

Regenerative Medicine and Stem Cell Therapy

Regenerative medicine and stem cell therapy represent innovative therapeutic strategies for kidney repair. Stem cells possess self-renewal capacity and the ability to differentiate into multiple cell types, making them valuable for tissue regeneration [41]. Embryonic stem cells have demonstrated the ability to integrate into renal tissues and contribute to kidney repair in experimental studies (Figure 4). Researchers are also developing kidney organoids, complex structures containing self-organizing renal cells that mimic natural kidney architecture. These advances may provide future solutions for replacing damaged kidney tissues and improving outcomes in patients with chronic kidney disease.

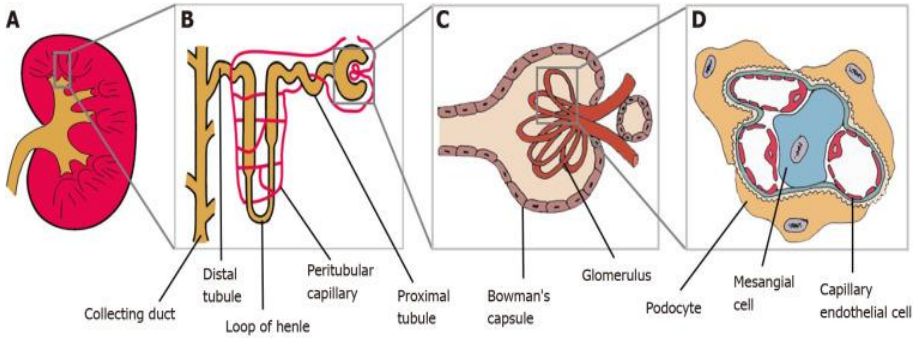

Figure 4: Kidney and its main components: A: Kidney; B: Magnification of the nephron; C: Renal corpuscle; D: Glomerulus. Podocytes, mesangial cells and capillary endothelial cells are parts of the glomerulus structure.

LIFESTYLE INTERVENTION AND PRESERVATION

Dietary Interventions in Chronic Kidney Disease

The kidneys play a critical role in maintaining fluid balance, electrolyte regulation, acid-base homeostasis, and removal of metabolic waste products. They also perform endocrine functions, including regulation of blood pressure, stimulation of red blood cell production, and activation of vitamin D for bone health. Dietary interventions are therefore essential in chronic kidney disease (CKD) management to reduce metabolic burden and preserve renal function [42]. Appropriate dietary modification, including controlled intake of sodium, potassium, phosphorus, and protein, helps slow disease progression and minimize complications. Lifestyle changes combined with nutritional management can significantly improve quality of life and reduce cardiovascular and metabolic risks in CKD patients (Figure 5).

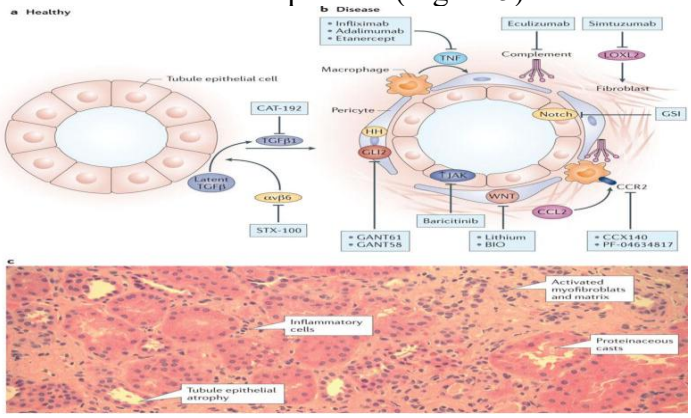

Figure 5: Targeting tubulointerstitial fibrosis in the treatment of CKD.

Conclusion

The development of novel therapies for chronic kidney disease (CKD) is urgently needed because mortality rates continue to rise despite advances in treatment. Recent research has identified promising therapeutic targets including fibrosis, inflammation, metabolic dysfunction, and vascular injury. Personalized approaches, such as the SONAR study, aim to improve treatment efficacy while minimizing adverse effects. Emerging strategies combining anti-inflammatory, metabolic, and genetic therapies may provide better outcomes, particularly for genetically linked conditions such as polycystic kidney disease and APOL1-associated nephropathy.

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