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Nuances of Chronic Kidney Disease (CKD) and Putative Remedial Measures

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Abstract: Chronic Kidney Disease (CKD) is a progressive condition where the kidney becomes damaged and loses its ability to filter blood and waste, leading to a buildup of toxins. This complex organ has intrinsic protective mechanisms that ensure systemic homeostasis in varying physiological and pathological conditions. Loss of these functions can lead to gradual loss of renal function, ending up in chronic kidney disease (CKD) which is a worldwide health problem. The gradual and usually irreversible reduction of glomerular filtration rate advances to end-stage renal disease (ESRD) if not addressed in a timely manner. CKD is almost always accompanied by other etiological factors like diabetes mellitus, hypertension, glomerulonephritis, polycystic kidney disease, obstructive nephropathy, infections, and drug-induced toxicity, all of these resulting in its progression. Owing to its multifactorial etiology, prevention and treatment measures need to be multidimensional. Foremost are the early detection, dietary and lifestyle changes, ideal pharmacologic treatment, and the use of nephroprotective foods, fruits, and herbal supplements having antioxidative, anti-inflammatory, and reno-protective effects. This article emphasizes the subtleties of CKD pathogenesis and presents a survey of evidence-based remedial interventions in an attempt to reduce progression and preserve renal function.

Keywords: Chronic kidney disease, Etiology, Herbal medicine, Lifestyle intervention, Nephroprotection.

Abbreviations

CKD	Chronic Kidney Disease
T2DM	Type 2 Diabetes Mellitus
ESRD	End-Stage Renal Disease
RAAS	Renin-Angiotensin-Aldosterone System
SGLT2	Sodium-Glucose Cotransporter 2
ADH	Antidiuretic Hormone
AGE	Advanced Glycation End-products
DCCT	Diabetes Control and Complications Trial
UKPDS	United Kingdom Prospective Diabetes Study
ADVAN	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
ARBs	Angiotensin II Receptor Blockers
GFR	Glomerular Filtration Rate
PDGF	Platelet-Derived Growth Factor
MPGN	Membranoproliferative Glomerulonephritis
GBM	Glomerular Basement Membrane
ANCA	Anti-Neutrophil Cytoplasmic Antibodies
PKD	Polycystic Kidney Disease
ADPKD	Autosomal Dominant Polycystic Kidney Disease
PKD2	Polycystic Kidney Disease 2
GANAB	Glucosidase II Alpha Subunit
PKHD1	Polycystic Kidney and Hepatic Disease 1
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
P-TEFb	Positive Transcription Elongation Factor b
BPH	Benign Prostatic Hyperplasia
IL-1β	Interleukin-1 Beta

IL-18	Interleukin-18
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor-alpha
VUR	Vesicoureteral Reflux
HIV	Human Immunodeficiency Virus
AKI	Acute Kidney Injury
TGF-β	Transforming Growth Factor-beta
PPIs	Proton Pump Inhibitors
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
COX	Cyclooxygenase
AIN	Acute Interstitial Nephritis
CIN	Contrast-Induced Nephropathy
SLE	Systemic Lupus Erythematosus
STZ	Streptozotocin
mTOR	Mechanistic Target of Rapamycin
HF	Heart Failure
CRS	Cardiorenal Syndrome
HFpEF	Heart Failure with Preserved Ejection Fractio
MRAs	Mineralocorticoid Receptor Antagonists
LVEF	Left Ventricular Ejection Fraction
LVAD	Left Ventricular Assist Devices
SOX9	SRY-Box Transcription Factor 9
RIPK3	Receptor-Interacting Protein Kinase 3
TEMP	Tolvaptan Efficacy and Safety in Management of Autosomal
GN	Glomerulonephritis
MRL	Murphy Roths Large
DKD	Diabetic Kidney Disease
HbA1c	Hemoglobin A1c
GLP-1	Glucagon-Like Peptide-1
MBD	Mineral and Bone Disorder
PM	Particulate Matter

I. Introduction

Chronic kidney disease (CKD) is a progressive and irreversible condition. In this case, the kidney is severely damaged over time, and unable to filter waste and excess fluid from the blood. Several causes are attributed to CKD which include diabetes, high blood pressure, autoimmune disorders, and kidney infections, besides certain medications. Early stages of CKD often have few symptoms, but as the disease progresses, symptoms can include foamy urine, swelling, fatigue, skin itching, and loss of appetite. CKD is a global health problem and is on the rise, occurring in almost 10% of the world's population and contributing heavily to morbidity, mortality, and healthcare expenses. It is distinguished by the slow and permanent deterioration of kidney function, which usually develops symptomatically silently until it reaches advanced phases (Jha *et al.*, 2023). The cause of CKD is multifactorial and includes both intrinsic renal and systemic diseases that compromise nephron integrity. Type 2 diabetes mellitus (T2DM) and hypertension are the two major causes, responsible for virtually two-thirds of CKD cases globally, with diabetic nephropathy being the most prevalent solitary cause of end-stage renal disease (ESRD). Infections like chronic pyelonephritis or recurrent urinary tract infections, chronic inflammation from metabolic syndrome or obesity, and autoimmune conditions like lupus nephritis and vasculitis also propel renal damage. The additional factors are polycystic kidney disease, obstructive nephropathy, long-term exposure to nephrotoxic agents, cardiovascular disease, and genetic susceptibility, all of which add to the risk of progression (Noble *et al.,* 2019). Pathophysiologic cascade of CKD includes hemodynamic stress, oxidative damage, low-grade chronic inflammation, and maladaptive repair of tissue, eventually resulting in interstitial fibrosis and glomerulosclerosis. With the loss of kidney function to control electrolytes, excrete metabolic waste products, and acid-base homeostasis, complications like anaemia, metabolic acidosis, hyperkalaemia, and mineral-bone disorder arise. These again worsen cardiovascular disease, which is still the leading cause of death among populations with CKD (Hill *et al.,* 2017). Traditional treatment for CKD aims to retard disease progression and minimize complications. Tightening glycaemic control in diabetic kidney disease, strict blood pressure control, and proteinuria reduction with RAAS inhibitors remain cornerstones. More recent pharmacological innovations like sodium-glucose cotransporter 2 (SGLT2) inhibitors and non-steroidal mineralocorticoid receptor antagonists have shown dual protective effects on the kidney and cardiovascular system. In addition to these, correction of anaemia, metabolic acidosis control, regulation of protein and electrolytes by diet, and strict fluid balance are a part of holistic evidence-based treatment plans. Nevertheless, since advances have been made, these treatments tend to centre on disease modification instead of global well-being and have prompted investigation of adjunctive natural methods (Dąbek *et al.,* 2023). Greater emphasis has been placed on herbal and home-based remedy treatments, especially in those areas where traditional medicine is interconnected with everyday healthcare routines. A number of spices and herbs are nephroprotective because of their antioxidant, anti-inflammatory, and antifibrotic mechanisms. Turmeric, which contains curcumin, diminishes inflammation systemically, ginger fights oxidative damage and garlic having sulphur-containing compounds reinforces renal and cardiovascular functions. Coriander, fennel, cumin, and basil provide alkaline-inducing effects, increase digestion, and serve as mild diuretics, assisting in urinary clearance. Hydration habits at home with plain water are still the safest, but barley water offers mild diuretic assistance and alkalinity (Chien

et al., 2019). Coconut water may provide electrolytes and hydration but should be restricted in advanced CKD owing to its potassium content. Increased water intake reduces antidiuretic hormone (ADH) levels in polycystic kidney disease, and this retards cyst growth. Fresh herbs are best used instead of concentrated supplements to prevent toxic build-up or medication interaction. CKD, in fact, is a multifactorial and intricate disease with various aetiologies and systemic implications (Narasaki *et al.*, 2020). It calls for an integrative approach based on traditional pharmacological therapies with safe and judicious use of herbal, dietary, and lifestyle interventions. This holistic approach not only treats the underlying disease processes but also improves overall health, slows disease progression, and enhances quality of life for CKD patients.

II. Causes of CKD

A. Diabetes Mellitus (Types 1 & 2)

Diabetes mellitus is the most common worldwide cause of chronic kidney disease (CKD) resulting in 40-66% of new end-stage renal disease (ESRD) in industrialized countries. This is the consequence of chronic hyperglycemia resulting in global prevalence of diabetes and progression of renal injury. Type 2 diabetes accounting for more than 90% of all known cases has become the leading cause of kidney failure. The global scenario of diabetes is staggering as we find a 1448% increase in Thailand, 981% in Russia, and 378% in the Philippines recorded between 2001 and 2015. Around 30-40% of diabetic patients ultimately develop CKD, and progression to diabetic nephropathy occurs in approximately 30% of Type 1 and 40% of Type 2 diabetics (Afkarian *et al.,* 2016). Prevalence studies establish equivalent rates of around 31% among Type 2 diabetic patients in China and Spain. The diabetic nephropathy pathogenesis is multifactorial, led by persistent hyperglycemia that overburdens renal glucose-processing pathways affecting the kidney. This way, 20–25% of glucose is released into the general circulation and almost 40% of gluconeogenesis, to glucose toxicity. Four key hyperglycemia-induced mechanisms are instrumental which include polyol pathway activation leading to sorbitol buildup and osmotic stress, advanced glycation end-product (AGE) accumulation leading to inflammation and fibrosis; protein kinase C activation resulting in vascular dysfunction and growth factor signalling; and increased flux through the hexosamine biosynthesis pathway stimulating inflammatory and fibrotic response. These biochemical alterations are reflected in the kidney due to structural changes. This includes glomerular basement membrane thickening, mesangial expansion with formation of Kimmelstiel-Wilson nodules, podocyte damage and loss, and diffuse vascular and tubulointerstitial damage like arteriolar hyalinosis, tubular atrophy, and interstitial fibrosis. Each of which increasingly compromises filtration capability leading to proteinuria (Forbes *et al.*, 2013; Edwards, 2014). The course of CKD differs between Type 1 and Type 2 diabetes, shaped by non-modifiable factors such as genetics, age, and diabetes duration and modifiable factors including poor glycaemic control (HbA1c >7.0%), hypertension, obesity, dyslipidemia, and smoking. Familial clustering and parental hypertension further increase risk, with peak prevalence over the age of 60. Landmark trials (DCCT, UKPDS, ADVANCE, Kumamoto) demonstrate that strict glycaemic control (HbA1c <7.0%) reduces incidence and progression of diabetic nephropathy, especially when combined with blood pressure control (<130/80 mmHg), lipid management, weight loss, smoking cessation, and nephroprotective pharmacotherapy such as ACE inhibitors, ARBs, and SGLT2 inhibitors. Diabetic kidney disease markedly elevates mortality, moderate albuminuria doubles to triples risk, severe albuminuria increases it nine-fold, and ESRD nearly 18-fold, largely through cardiovascular events (Fig. 1).

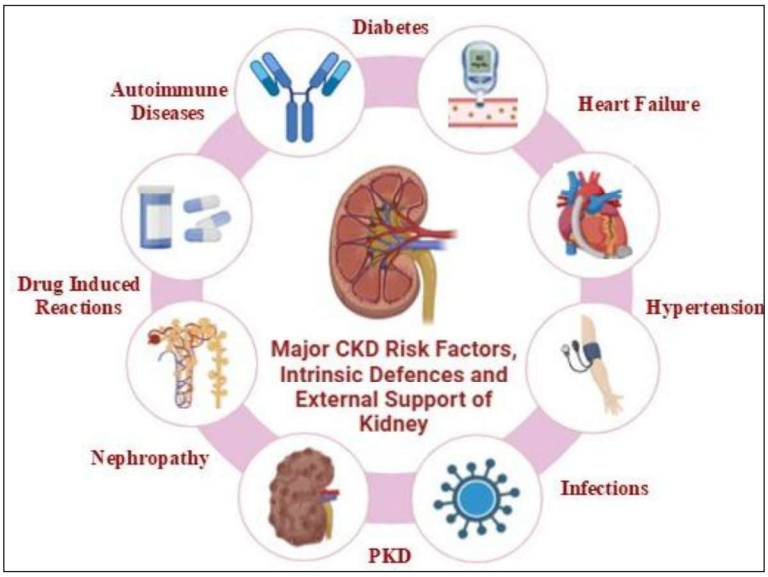

Fig. 1: Major Risk Factors Contributing to Chronic Kidney Disease (CKD) Created Using Biorender.com

B. Heart Failure

The interaction between chronic kidney disease (CKD) and heart failure (HF) gives rise to one of the most complicated clinical situations. This is a bidirectional pathophysiological cascade known as cardiorenal syndrome (CRS). This aggravates prognosis and enhances mortality risk (Ronco *et al.,* 2008). CRS is divided into five categories, of which Type 2 (chronic HF to CKD) and Type 4 (CKD to HF) are most pertinent. In Type 2, fluid overload and increased central venous pressure, as opposed to decreased cardiac output per sec, compromise glomerular filtration and enhance renal damage, even in the setting of preserved ejection fraction (Ronco *et al.,* 2008). In Type 4, CKD speeds up cardiac dysfunction by uremic toxins, inflammation, oxidative stress, mineral bone disorder, and sympathetic overdrive, leading to left ventricular hypertrophy, observed in as many as 80% of end-stage CKD patients (Zoccali *et al.,* 2023). Neurohormonal activation of RAAS and sympathetic nervous system drives damage through oxidative stress, fibrosis, and hypertrophy, fueling renal and cardiac deterioration. Clinically, the presence of CKD and HF reduces prognosis, cardiovascular disease being responsible for 40–50% of mortality in advanced CKD, as opposed to 26% in normal kidney function (Cruz *et al.,* 2013). Patients with HF and advanced CKD have increased hospitalization, readmission, and mortality rates, where HFpEF being very common. Management needs a multi-pronged approach, such as RAAS inhibitors, that postpone dialysis even without a survival advantage in severe CKD. SGLT2 inhibitors that are strong cardiorenal protectants regardless of diabetes; beta-blockers, that are mortality-reducing even in the cases that are on dialysis; and MRAs, which reduce cardiovascular and all-causes of mortality need strict hyperkalemia monitoring (Cruz *et al.,* 2013). Diuretics continue to play a vital role in volume management, with loop diuretics as the first line and thiazide-like diuretics such as chlorthalidone being effective even in stage 4 CKD, albeit with close observation. Further, cardiac resynchronization therapy (CRT) advances eGFR, LVEF, and survival, and LVADs provide hemodynamic support but with mixed renal effects and increased mortality in ESRD (Hakopian *et al.,* 2019). Life-style and dietary interventions, such as exercise, blood pressure management, and restriction of protein intake (0.6–0.8 g/kg/day, best achieved with a plant-based diet) enhance both renal and cardiovascular functions. Newer therapies, including Klotho pathway agonists, SOX9 blockers, RIPK3 antagonists, and AI-based personalization are promising, while SGLT2 inhibitors, RAAS inhibition, and MRAs in combination may afford synergistic protection. In general, optimal management necessitates individualized, multi-dimensional approaches weighing therapeutic benefit against risk, with new pharmacologic and device-based therapies bringing new promise for enhanced outcomes in this high-risk group (Arora *et al.,* 2020).

C. Hypertension

Hypertension damages kidneys through the narrowing, hardening, and constriction of arteries, leading to reduced blood supply and compromised filtration function. The vascular damage results in albuminuria (protein leakage from the blood into urine) and decreased glomerular filtration rate (GFR). Both of which are crucial indicators of hypertensive nephropathy. Chronic high blood pressure puts tension on tiny kidney arteries, producing endothelial damage, loss of elasticity, and arteriosclerosis, which impair the filtering ability of the kidney. Glomerular damage breaks the filter barrier, leading to protein leakage into urine and hampering the removal of waste, giving rise to decreased GFR. This generates a vicious cycle whereby deficient kidney functioning results in water retention and adds to an increase in blood pressure, further hastening its damage. Signs of hypertensive kidney damage include albuminuria or proteinuria secondary to podocyte and glomerular capillary damage, reduced GFR indicating vascular and nephron damage, and in a minority of cases, fluid overload and electrolyte disturbances. Failure to intervene promptly may lead to CKD or ESRD. Early detection and optimal control of blood pressure are essential for maintaining renal function and retarding progression of CKD (Beevers *et al.,* 2001).

D. Glomerulonephritis

Glomerulonephritis is an immune-mediated glomerular inflammation involving both humoral and cell-mediated immune mechanisms that frequently results in fibrosis. It can result from autoimmune disease or infectious causes. The pathogenic mechanism involves immune-mediated damage to the glomerular basement membrane, mesangium, or capillary endothelium, with coagulation cascade activation and complement system activation being important components. Inflammatory cascades deliver cytokines such as platelet-derived growth factor (PDGF), causing mesangial proliferation and glomerulosclerosis, whereas T lymphocytes and macrophages are responsible for direct tissue injury. Of its forms, IgA nephropathy is most prevalent, resulting from galactose-deficient IgA1 immune complex deposition within the glomerulus, through a four-hit model of abnormal IgA1 production, autoantibody formation, immune complex deposition, and mesangial activation (Suzuki *et al.,* 2011). The alternative complement pathway is at the centre of this process. Post-infectious glomerulonephritis, usually after streptococcal infections, is a consequence of the formation and deposition of immune complexes in the glomeruli, with typical "lumpy bumpy" IgG, C3 and subepithelial "hump-type" deposits. The disease is persistent in some patients due to defects in complement regulation (Sethi *et al.,* 2012). Membranoproliferative glomerulonephritis (MPGN) is characterized by mesangial proliferation and thickening of the capillary wall, classified into three types. Type I (immune complex-mediated, classical pathway), Type II (dense deposit disease secondary to uncontrolled alternative pathway activation, frequently associated with C3 nephritic factor), and Type III (with further sub-epithelial deposits). Crescentic glomerulonephritis is a very severe, rapidly progressive type with more than 50% of the glomeruli showing crescents due

to endothelial damage, glomerular basement membrane disruption, and fibrin deposition causing proliferation of parietal epithelial cells and glomerular obliteration. It consists of three broad categories: anti-GBM disease (linear IgG deposition), immune complex-mediated (granular deposits in disease such as lupus or IgA nephropathy), and pauci-immune ANCA-associated one (most prevalent in adults). Macrophages, CD4+ T cells, and Th17 pathways are central to the crescent formation. Prognosis is varied: post-infectious glomerulonephritis resolves in children within 6–8 weeks but 1-2% will go on to develop chronic disease, while crescentic glomerulonephritis is a clinical emergency that often results in end-stage renal disease if not given prompt immunosuppressive therapy (Couser *et al.,* 2012).

E. Polycystic Kidney Disease (PKD)

Polycystic kidney disease (PKD) is a genetic disorder that is caused by the growth of several fluid-filled cysts within the kidneys, resulting in progressive kidney enlargement and loss of renal function. PKD is the fourth leading cause of end-stage renal disease and affects 1 in 400-1,000 people worldwide. PKD has two principal forms: autosomal dominant PKD (ADPKD), responsible for 85-90% of cases, and autosomal recessive PKD (ARPKD), much less common. ADPKD is usually due to mutation of the *PKD1* gene (85%) encoding polycystin-1 or the *PKD2* gene (15%) encoding polycystin-2, with a few instances due to *GANAB* mutations. It has a dominant inheritance, a 50% risk of transmission (Cornec *et al.,* 2018). ARPKD is caused due to mutation of the *PKHD1* gene encoding fibrocystin and requires both alleles to be affected, and parents tend to be asymptomatic carriers. At the molecular level, the "two-hit" theory accounts for cyst development in ADPKD, when an inherited mutation in *PKD1/PKD2* is followed by a somatic mutation in the remaining allele of renal epithelial cells. The polycystin-1/polycystin-2 complex, which is located in primary cilia, is important for mechanosensation and calcium signalling, and its aberration results in dysregulated intracellular calcium levels, dysregulated cAMP signalling, and increased cell proliferation. In like manner, fibrocystin in ARPKD localizes to cilia and controls adhesion, proliferation, and mitochondrial function (Bergmann *et al.,* 2018). Cyst growth in ADPKD usually happens after it becomes severed from nephrons, fluid secretion being triggered by cAMP-mediated chloride transport through CFTR, while ARPKD cysts are attached to the nephron and grow via dysregulated sodium reabsorption. Clinically, ADPKD becomes apparent during adulthood, with kidney failure appearing at ages 55–75 (with gene mutation dependence), whereas ARPKD occurs in infancy or early childhood, usually leading to renal failure by age 15 and often with congenital hepatic fibrosis. Therapeutically, the inhibition of cAMP signalling with tolvaptan, a vasopressin V2 receptor antagonist, has been effective in slowing down ADPKD progression, whereas novel strategies involve microRNA modulation, *P-TEFb* kinase inhibition, and correction of mitochondrial function. Overall, PKD reflects the intricacy of genetic heterogeneity, cellular pathways, and mechanisms of cystogenesis, requiring gene- and pathway-specific therapeutic approaches (Torres *et al.,* 2012).

F. Obstructive Nephropathy

Obstructive nephropathy is a significant and potentially reversible contributor to chronic kidney disease (CKD), accounting for nearly 10% of both acute and chronic cases, and arises from structural or functional barriers that impede urinary flow, initiating a cascade of pressure-induced, hemodynamic, and molecular mechanisms that progressively damage renal parenchyma. Common aetiologies include kidney stones, benign prostatic hyperplasia (BPH), and malignancies. Kidney stones are a leading cause of acute obstruction in middle-aged adults, with stone-induced nephropathy linked to both direct obstruction and crystalline toxicity; calcium oxalate crystals induce mitochondrial dysfunction, oxidative stress, and inflammasome-mediated immune activation, while mechanical blockage elevates intratubular pressure, reduces renal blood flow, and ultimately leads to interstitial fibrosis and nephron loss (Nørregaard *et al.,* 2023). BPH is the most prevalent cause of obstructive nephropathy in elderly men, resulting from urethral compression and bladder outlet obstruction. This leads to urinary retention, infections, bladder stones, and progressive renal impairment, with epidemiological studies showing strong associations between bladder outlet obstruction and CKD risk. Malignancies, particularly prostate (20%), bladder (18%), colorectal (10%), lymphoma (8%), breast (4%), and gynaecological cancers, also contribute to ureteral obstruction, with malignant retroperitoneal fibrosis carrying especially poor prognosis, often limiting survival to just a few months (Artiles *et al.,* 2023). Patho physiologically, obstruction initiates elevated hydrostatic pressure in the collecting system, increasing intraglomerular pressure and impairing glomerular filtration. These compensatory hemodynamic phases are characterized initially by prostaglandin-mediated vasodilation, followed by progressive vasoconstriction driven by thromboxane A2 and angiotensin II, and eventually marked by hypo- perfusion with sharp GFR decline (Klahr *et al.,* 1994). At the cellular level, tubular stretching and rupture trigger proinflammatory cytokine release (IL-1β, IL-18, IL-6, TNF-α), chemokine recruitment, and activation of the renin–angiotensin–aldosterone system (RAAS), with angiotensin II driving fibrotic remodelling. Oxidative stress, tubular ischemia, and loss of peritubular capillaries exacerbate interstitial fibrosis, the final common pathway of chronic obstructive nephropathy. This is characterized by leukocyte infiltration, vascular dysfunction, capillary rarefaction, hypoxia, and irreversible transformation of glomeruli into atubular forms up to 80% after 14 days of complete obstruction (Chevalier *et al.,* 2009). Functionally, obstruction impairs sodium reabsorption; down regulates aquaporin's leading to impaired urinary concentrating ability and postobstructive polyuria, and disrupts hydrogen ion

secretion causing distal renal tubular acidosis. Prognosis largely depends on duration, severity, and laterality of obstruction, as well as infection status, with short-term obstruction permitting full recovery and prolonged cases causing permanent loss of function. Experimental models confirm that kidney function may persist for up to two weeks following ureteral ligation but rarely beyond four weeks. Importantly, post-obstructive diuresis occurs in nearly half of patients after decompression, serving an adaptive role in solute elimination but carrying risks of dehydration, electrolyte imbalance, and hypovolemic shock if unmonitored. Therefore, early recognition and prompt relief of obstruction are critical to halting progressive fibrosis, preserving renal function, and preventing progression to end-stage renal disease (Klahr and Morrissey, 2002).

G. Infections

Infections are an underappreciated etiology of chronic kidney disease (CKD), a classical example of which is recurrent pyelonephritis. Recurrent infections of the kidney induce acute inflammation, which, if prolonged, advances to chronic tubulointerstitial damage, fibroblast activation, collagen deposition, tubular atrophy, calyceal deformity, and loss of corticomedullary architecture. Clinically, chronic pyelonephritis presents as small, scarred kidneys with irregular pyelocalyceal systems, worsening renal function, proteinuria, and hypertension (Lane *et al.,* 2011). Risk factors include vesicoureteral reflux (VUR), urinary obstruction, diabetes, immunosuppression, and congenital abnormalities. VUR is especially important, raising the risk of renal scarring almost four times in children, particularly under five years of age. Outside pyelonephritis, bacterial (post-streptococcal glomerulonephritis, associated with endocarditis, renal tuberculosis), viral (hepatitis B/C, HIV, Hantavirus), and parasitic infections (schistosomiasis, malaria, leptospirosis) cause CKD. Sepsis-induced AKI also commonly evolves into CKD because of microcirculatory failure and chronic inflammation (Chawla *et al.,* 2011). Patho physiologically, infection-induced CKD is mediated by inflammatory cascades with recruitment of neutrophil, cytokine release (IL-1, IL-6, TGF-β), fibroblast-to-myofibroblast differentiation, extracellular matrix deposition, and complement dysregulation. Early identification, prompt treatment of the infection, management of VUR, surgical repair of anatomical abnormality, and administration of ACE inhibitors or ARBs for the control of proteinuria and hypertension can reduce morbidity. Prognosis is variable as early treatment can permit recovery, but tardy or repetitive trauma can cause progression to CKD resulting in end-stage renal disease (Kurts *et al.,* 2013).

H. Drug-Induced Nephropathy

Drug-induced nephropathy is preventable but cases of acute kidney injury (AKI) may lead to chronic kidney disease (CKD). Frequent offenders are NSAIDs, contrast dyes, antibiotics, proton pump inhibitors (PPIs), and chemotherapeutic nephrotoxins like Cisplatin. NSAIDs induce damage through hemodynamic processes whereas COX inhibition lowers prostaglandin production. This results in medullary hypoxia, tubular necrosis, and prerenal azotemia. Through immune-mediated acute interstitial nephritis (AIN) with T-cell–mediated interstitial infiltration; risk factors are advanced for CKD. This leads to volume depletion, cardiovascular disease, and concomitant RAAS blockade or diuretic conditions (Perazella *et al.,* 2018). Contrast-induced nephropathy (CIN) occurs due to vasoconstriction, medullary hypoxia, reactive oxygen species, mitochondrial damage, and elevated blood viscosity. This usually happens in those cases with baseline eGFR <60 mL/min/1.73 m² and exacerbated by diabetes, heart failure, and polypharmacy. Further, Mehran score facilitates risk stratification. The Mehran risk score is used to predict a patient's risk of developing contrast-induced nephropathy (CIN), now commonly called contrast-associated acute kidney injury (CA-AKI). Aminoglycosides concentrate in proximal tubules, leading to oxidative damage, non-oliguric AKI, and electrolyte wasting, whereas vancomycin can cause tubular cast formation. Further, β-lactams, fluoroquinolones, and PPIs largely cause AIN through immune-mediated hypersensitivity, with PPIs additionally facilitating CKD advancement through indoxyl sulphate deposition and chronic inflammation (Radi *et al.,* 2019). Cisplatin nephrotoxicity is characterized by proximal tubule accumulation, DNA injury, oxidative stress, and cytokine-induced inflammation, resulting in tubular necrosis. Wasting of magnesium, and CKD risk is based on cumulative dose, hydration, age, and concomitant nephrotoxins. Prevention is achieved through risk assessment, dose optimization, hydration regimens (normal saline or sodium bicarbonate for CIN), once-daily aminoglycosides monitoring, and early discontinuation of offending drugs. Corticosteroids can be helpful for biopsy-proven AIN. The prognosis is variable and NSAID hemodynamic damage is generally reversible, AIN recovers in 50-60% of cases treated with steroids. Aminoglycoside damage is often followed by residual dysfunction, and Cisplatin commonly leads to permanent CKD. Early diagnosis and drug stewardship are important to avert the advancement to end-stage renal disease (Perazella *et al.,* 2018).

I. Autoimmune Diseases

Autoimmune diseases, particularly lupus nephritis and vasculitis, are important causes of kidney injury that can lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD). The unifying mechanism is immune complex deposition and complement activation within the glomeruli, which initiates inflammation and progressive structural damage. In lupus nephritis, a manifestation of systemic lupus erythematosus (SLE), immune complexes composed of IgG, IgM, complement components (C3, C1q), and nuclear antigens accumulate in the mesangium, capillary loops, or along the glomerular basement membrane (Hahn *et al.,* 2012). This immune complex localization is responsible for the heterogeneity of histological classes observed in renal

biopsies. Vasculitic disorders, including ANCA-associated and cryoglobulinemic associated ones damage the kidneys through immune complex deposition and small vessel inflammation, resulting in glomerular necrosis, crescent formation, and rapidly progressive glomerulonephritis. The pathogenic cascade begins with antibody–antigen complex formation, either in circulation or *in situ* within the glomerulus. These complexes activate complement, generating C5b-9 membrane attack complexes that promote recruitment of neutrophils, macrophages, and mononuclear cells. Inflammatory mediators such as TNF-α, IL-1, and IL-6 further amplify the response, causing endothelial injury, mesangial proliferation, and disruption of podocyte integrity. Functionally, this manifests as proteinuria, hematuria, edema, and declining glomerular filtration (Kitching *et al.,* 2020). Chronic exposure to ongoing immune injury fosters tubulointerstitial inflammation, capillary rarefaction, and progressive fibrosis, the final pathway leading to irreversible renal failure. Histopathologically, autoimmune glomerulonephritis is defined by immune deposits detectable on immunofluorescence and electron microscopy, often accompanied by proliferative and sclerotic lesions (Table I). The clinical trajectory is variable, ranging from asymptomatic urinary abnormalities to fulminant rapidly progressive glomerulonephritis. Without timely immunosuppressive therapy, continuous immune complex deposition drives scarring, nephron loss, and progression to ESRD (Couser *et al.,* 2012).

Table I: Comprehensive Evidence Based Mapping of CKD Aetiologies Based on Animal and Human Studies

Cause	*Study Type*	*Model/Population*	*Key Findings*	*Treatment*	*Outcomes*	*Reference*
Diabetes Mellitus (Type 2)	Animal Study	STZ mice (Streptozotocin-induced)	Mild-to-moderate albuminuria, mild glomerular and tubular damage, no hypertension or glomerulosclerosis	Various drug treatments tested	Simulates early-stage diabetic nephropathy	(Pointeau *et al.,* 2025)
	Human Study	UKPDS Cohort	Tight glycemic control reduces microvascular complications; limited effect on macrovascular outcomes	Sulfonylureas, Insulin, Metformin	Reduced microvascular disease, modest cardiovascular benefit with metformin	(UKPDS, 1993)
Hypertension	Animal Study	Spontaneously Hypertensive Rats	Progressive glomerulosclerosis, proteinuria, and renal interstitial fibrosis	ACE inhibitors, ARBs	Reduced renal injury and prolonged survival	(Feld *et al.,* 1990)
	Human Study	AASK Trial (African American Study of Kidney Disease)	Intensive BP control slowed CKD progression	ACE inhibitors vs Beta-blockers	Ramipril reduced CKD progression more effectively	(Agodoa *et al.,* 2001)
Glomerulone-phritis	Animal Study	Anti-GBM nephritis rat model	Immune complex deposition leads to crescentic GN	Cyclophosphamide, steroids	Ameliorated renal damage	(Sadeghi *et al.,* 2018)
	Human Study	Cochrane Review of GN treatments	Immunosuppressives improve renal outcomes in proliferative GN	Corticosteroids, Cyclophosphamide	Improved renal survival	(Tunnicliffe *et al.,* 2018)
Polycystic Kidney Disease (PKD)	Animal Study	Pkd1 knockout mouse	Massive cyst formation, kidney enlargement, renal failure	mTOR inhibitors, vasopressin V2 receptor antagonists	Slowed cyst growth	(Shillingford *et al.,* 2010)
	Human Study	TEMPO 3:4 Trial	Tolvaptan slowed eGFR decline and kidney volume increase	Vasopressin V2 receptor antagonist (Tolvaptan)	Delayed disease pro-gression	(Torres *et al.,* 2012)
Obstructive Nephropathy	Animal Study	Unilateral ureteral obstruction rat	Tubulointerstitial fibrosis, inflammation	Anti-fibrotic agents, ACE inhibitors	Reduced fibrosis and preserved function	(Schanstra *et al.,* 2003)
	Human Study	Children with posterior urethral valves	Relief of obstruction improved renal outcomes	Surgical intervention	Better renal prognosis with early relief	(Coquillette *et al.,* 2020)

Cause	Study Type	Model/Population	Key Findings	Treatment	Outcomes	Reference
Infections	Animal Study	Mouse model of pyelonephritis	Ascending infection caused interstitial nephritis	Antibiotic therapy	Prevented chronic scarring	(Olson *et al.,* 2017)
	Human Study	Post-streptococcal GN cases	Immune-mediated GN after streptococcal infection	Supportive therapy, antibiotics	Most recover, some progress to CKD	(Alhamoud *et al.,* 2021)
Drug-Induced Nephropathy	Animal Study	Cisplatin-treated rats	Acute tubular necrosis, oxidative stress	Antioxidants, nephroprotective agents	Reduced nephrotoxicity	(Khairnar *et al.,* 2020)
	Human Study	Patients on NSAIDs	Chronic interstitial nephritis, papillary necrosis	Drug withdrawal	Improved renal function after cessation	(Kleinknecht, 1995)
Autoimmune Diseases	Animal Study	MRL/lpr mouse (lupus model)	Immune complex-mediated GN resembling lupus nephritis	Immunosuppressives (MMF, cyclophosphamide)	Reduced renal injury	(Lui *et al.,* 2002)
	Human Study	ALMS Trial (Lupus Nephritis)	MMF vs Cyclophosphamide for induction therapy	Immunosuppressives	MMF non-inferior to cyclophosphamide, fewer side effects	(Appel *et al.,* 2009)

III. Environmental and Lifestyle Factors

Environmental and lifestyle determinants have significant impacts on the development and advancement of chronic kidney disease (CKD), either through direct generation of nephrotoxic effects or indirect exacerbation of comorbid conditions like hypertension, diabetes, and cardiovascular disease. These include smoking, where it is evidenced that current smokers are 63% more likely to have CKD than non-smokers, and severe smokers who have over 30 pack-years have up to a 2.6-fold elevated risk. Smoking hurts the kidney by inducing vascular injury, glomerular impairment, oxidative stress, chronic inflammation, renin-angiotensin system dysregulation, and rapid renal vascular aging. Equally, obesity is an independent risk factor for CKD, and it raises the risk of albuminuria by 51% and low eGFR by 28%. The pathophysiology involves hemodynamic changes caused by obesity like glomerular hyper- filtration, podocyte damage, and glomerulosclerosis, metabolic disturbances including lipid derangements, insulin resistance, adipokine imbalance, and oxidative stress and Lipotoxicity to the kidneys resulting in mitochondrial damage, tubular cell cytotoxicity, and renal interstitial fibrosis (Briffa *et al.,* 2013). Excessive dietary salt also promotes CKD risk by promoting sodium-sensitive hypertension, activating intrarenal angiotensin-II generation, increasing inflammation and oxidative stress, and facilitating proteinuria, fluid overload, and cardiovascular load. Enduring dehydration and heat stress, especially among agricultural labourers, are also other new aetiologies of CKD. This involves intermittent subclinical ischemic kidney damage from elevation of vasopressin, fructokinase-mediated oxidative stress, hyperuricemia, and attenuated renal perfusion leading to renal fibrosis and chronic progression. Environmental pollution is a significant contributory factor, with exposure to particulate matter (PM2.5 and PM1), heavy metals like lead, cadmium, arsenic, and mercury and industrial contaminants. These agents induce oxidative stress, inflammation, endothelial dysfunction, and direct cellular toxicity to renal tissues (Lopez *et al.,* 2011). Occupational hazards add to these risks since employees engaged in agriculture, mining, and manufacturing often experience chronic heat stress, exposure to pesticides, and nephrotoxic chemicals, leading to subclinical or overt kidney damage. Additionally, drug-induced nephrotoxicity though preventable still causes CKD. Chronic NSAID therapy results in prostaglandin suppression and hemodynamically mediated renal injury. Whereas antimicrobials, ACE inhibitors, ARBs, and some statins may induce tubular toxicity, interstitial nephritis, intraglomerular hemodynamic alterations, or rhabdomyolysis. With these multifactorial risks, preventive interventions targeting modifiable factors are essential. Lifestyle changes like stopping smoking, exercise, sodium limitation, greater consumption of fruits and potassium-rich foods, and proper hydration have all been demonstrated to substantially reduce CKD risk (Kalantar *et al.,* 2021). Furthermore, occupational protective measures and environmental protection policies both have pivotal roles to play in limiting population-level exposures to nephrotoxins. These findings warrant the targeting of environmental and lifestyle determinants of CKD with broad, multi-level interventions beyond traditional medical therapy. This may include public health interventions and patient-managed lifestyle modification (Table II).

TABLE II: GENETIC AND MOLECULAR LANDSCAPE OF CHRONIC KIDNEY DISEASE ACROSS DIVERSE AETIOLOGIES

Sr. No	*Diseases*	*Genes*	*Function / Pathway*	*Relevance to the Disease*	*Relevance in CKD*	*Reference*
1.	Diabetes	ACE	Renin–angiotensin–aldosterone system (RAAS) regulation	Linked to insulin resistance and hypertension in diabetes	Major gene for diabetic nephropathy and progression of CKD	Sawaf *et al.,* 2023, Pandey *et al.,* 2023, Ali *et al.,* 2024 Groopman *et al.,* 2018, Köttgen *et al.,* 2022, Boima *et al.,* 2025, Sandholm *et al.,* 2023
		AGT	Precursor in RAAS	Involved in hypertension risk in diabetes	Associated with renal fibrosis and CKD progression	
		NOS3	Nitric oxide production, vascular homeostasis	Dysfunction linked to endothelial injury in diabetes	Endothelial dysfunction → glomerulosclerosis, CKD	
		SLC2A1	Glucose transporter	Key role in glucose uptake	Overexpression in kidney mesangial cells → diabetic nephropathy	
		TGFB1	Fibrosis, inflammation	Promotes islet fibrosis and β-cell apoptosis	Central mediator of renal fibrosis in CKD	
		IL6	Pro-inflammatory cytokine	Inflammation in insulin resistance & T1D autoimmunity	Contributes to kidney inflammation and CKD	
		TNF	Inflammatory signaling	Impaired insulin signaling	Causes podocyte injury and CKD progression	
		APOE	Lipid metabolism & inflammation	Dyslipidemia and insulin resistance	Dyslipidemia-driven CKD, vascular injury	
		PPARG	Insulin sensitivity regulator	T2D susceptibility gene	Impacts renal hemodynamics and inflammation	
		HLA-DR3, DR4	Antigen presentation	Strongly linked to T1D susceptibility	Linked to autoimmune-mediated renal damage (CKD risk in T1D)	
2.	Heart Failure	ACE	RAAS regulation → vasoconstriction, sodium retention	ACE polymorphisms linked to HF progression, cardiac remodeling	Major gene for diabetic & hypertensive nephropathy; accelerates CKD	
		AGT	Precursor of angiotensin II	Contributes to cardiac hypertrophy and HF	Associated with renal fibrosis and CKD progression	
		AGTR1	Mediates angiotensin II effects (vasoconstriction, fibrosis)	Involved in LV hypertrophy and systolic dysfunction	Promotes glomerulosclerosis and renal fibrosis	
		NPPA (Atrial Natriuretic Peptide)	Natriuresis, vasodilation, RAAS suppression	Variants affect susceptibility to HF and fluid overload	Important for sodium balance and CKD progression	

Sr. No	*Diseases*	*Genes*	*Function / Pathway*	*Relevance to the Disease*	*Relevance in CKD*	*Reference*
		NPPB	Biomarker of cardiac stress, regulates sodium excretion	Overexpressed in HF as a compensatory mechanism	Elevated in CKD due to volume overload and impaired clearance	
		NOS3	Endothelial function, vascular tone	Dysfunction → endothelial injury in HF	Endothelial dysfunction → CKD progression	
		TGFB1	Fibrosis, extracellular matrix regulation	Promotes cardiac fibrosis and remodeling	Major driver of renal fibrosis and CKD	
3.	Hypertension	ACE	Converts Ang I → Ang II (RAAS)	ACE polymorphisms (esp. I/D) strongly linked to hypertension	Accelerates CKD via RAAS overactivation and glomerular injury	
		AGT	Angiotensin precursor	Variants (M235T) increase plasma AGT → higher BP	Associated with renal fibrosis and CKD progression	
		AGTR1	Mediates Ang II effects: vasoconstriction, fibrosis	Strongly implicated in essential hypertension	Drives renal injury, glomerulosclerosis, and CKD	
		REN	Rate-limiting enzyme in RAAS	Variants influence renin activity → hypertension risk	Dysregulated renin activity promotes CKD progression	
		NOS3	Produces nitric oxide, regulates vascular tone	Polymorphisms → endothelial dysfunction & hypertension	Endothelial dysfunction accelerates kidney damage	
		ADD1	Regulates sodium reabsorption in renal tubules	Gly460Trp polymorphism linked to salt-sensitive hypertension	Sodium retention contributes to CKD	
		CYP11B2	Produces aldosterone	−344T/C variant → higher aldosterone levels, hypertension	Excess aldosterone → renal fibrosis and CKD	
		NPPA	Sodium excretion, vasodilation	Mutations reduce natriuretic effect, contributing to hypertension	Dysregulation worsens CKD-related sodium/fluid overload	
		UMOD	Tubular protein affecting sodium transport	Variants increase salt-sensitive hypertension	Risk gene for CKD progression and tubular injury	
		TGFB1	Fibrosis & ECM regulation	Contributes to vascular remodeling in hypertension	Major mediator of renal fibrosis in CKD	
4.	Glomerulonephritis	HLA Class II (HLA-DQA1, HLA-DQB1, HLA-DRB1)	Antigen presentation, adaptive immunity	Strongly linked to autoimmune GN (e.g., IgA nephropathy, membranous nephropathy)	Autoimmune-mediated renal injury → CKD	

Sr. No	*Diseases*	*Genes*	*Function / Pathway*	*Relevance to the Disease*	*Relevance in CKD*	*Reference*
		CFH	Regulates complement activation	Mutations → uncontrolled complement activation in GN	Contributes to CKD via complement-mediated glomerular injury	
		C3	Complement cascade activation	Overactivation leads to immune complex deposition	Promotes glomerular inflammation → CKD progression	
		TNFA	Inflammatory cytokine	Mediates glomerular inflammation and apoptosis	Drives renal fibrosis and CKD progression	
		IL6	Pro-inflammatory cytokine	Elevated in GN → mesangial proliferation and inflammation	Contributes to renal injury and CKD progression	
		TGFB1	Fibrosis and ECM deposition	Promotes glomerular sclerosis in GN	Central driver of renal fibrosis in CKD	
		NPHS1	Podocyte slit diaphragm protein	Mutations → proteinuria, glomerulosclerosis	Loss of nephrin → CKD progression	
		NPHS2	Podocyte function and slit diaphragm integrity	Mutations → steroid-resistant nephrotic syndrome, GN	Podocyte injury → CKD progression	
		ACE	RAAS, fibrosis	RAAS contributes to glomerular hypertension in GN	RAAS activation accelerates CKD progression	
		PLCG2	B-cell signaling	Autoimmune GN susceptibility	Chronic immune activation → CKD	
5.	Polycystic Kidney Disease	PKD1	Encodes polycystin-1, involved in cilia function and cell signaling	Mutations → Autosomal Dominant PKD (ADPKD), cyst formation	Progressive cystic renal damage → CKD	
		PKD2	Encodes polycystin-2, calcium channel	Mutations → ADPKD, cyst expansion	Tubular dysfunction → CKD progression	
		PKHD1	Encodes fibrocystin, involved in cilia and tubular integrity	Mutations → Autosomal Recessive PKD (ARPKD)	Tubular injury and fibrosis → CKD	
		GANAB	Glucosidase II subunit, protein processing in ER	Mutations → PKD with mild cystic disease	ER stress contributes to CKD progression	
		DNAJB11	ER co-chaperone, protein folding	Mutations → atypical PKD	Contributes to cyst formation and CKD	
		HNF1B	Transcription factor regulating kidney development	Mutations → renal cysts, developmental anomalies	Congenital kidney disease progressing to CKD	

Sr. No	*Diseases*	*Genes*	*Function / Pathway*	*Relevance to the Disease*	*Relevance in CKD*	*Reference*
		TSC1/TSC2	mTOR signaling, cell proliferation	Mutations → renal cysts and angiomyolipomas	mTOR-mediated tubular proliferation → CKD	
		UMOD	Tubular protein regulating sodium handling	Variants → predispose to cystic kidney changes	Tubular injury and CKD progression	
		ACE	RAAS, fibrosis	RAAS overactivity worsens cystic hypertension	Accelerates CKD via fibrosis and glomerular stress	
		TGFB1	Fibrosis and extracellular matrix	Promotes cyst expansion and interstitial fibrosis	Major mediator of CKD progression	
6.	Obstructive Nephropathy	TGFB1	Fibrosis, extracellular matrix deposition	Central mediator of tubular and interstitial fibrosis in obstruction	Key driver of renal fibrosis in CKD	
		ACE	RAAS, fibrosis, vascular tone	RAAS activation worsens tubular injury and fibrosis	Promotes CKD progression through glomerulosclerosis	
		MMP2 / MMP9	ECM remodeling	Upregulated in obstructive nephropathy; involved in fibrosis and tubular remodeling	ECM dysregulation contributes to CKD	
		IL6	Pro-inflammatory cytokine	Elevated in response to obstruction-induced inflammation	Drives renal inflammation in CKD	
		TNF	Inflammatory and apoptotic signalling	Promotes tubular apoptosis and interstitial inflammation	Contributes to CKD progression	
		CTGF	Fibrosis, ECM regulation	Works downstream of TGFB1 to promote fibrosis in obstruction	Major mediator of CKD-related fibrosis	
		HAVCR1 / KIM-1	Marker and mediator of tubular injury	Highly upregulated in obstructed tubules	Marker and contributor to CKD progression	
		COL1A1 / COL3A1	ECM components	Upregulated during fibrosis in obstruction	Accumulation → CKD progression	
		NFKB1	Transcription factor for inflammation	Activated by obstruction-induced stress	Chronic activation → CKD inflammation and fibrosis	
		PPARG	Anti-inflammatory and metabolic regulation	Protective in tubular injury models	Modulates CKD progression and fibrosis	
7.	Infection-Related Kidney Disease	TLR4	Innate immune receptor	Recognizes bacterial LPS → triggers inflammatory response in infection	Chronic activation → tubular inflammation and CKD progression	
		TLR2	Pathogen recognition, innate immunity	Recognizes gram-positive bacteria → triggers renal inflammation	Contributes to CKD via chronic immune activation	

Sr. No	*Diseases*	*Genes*	*Function / Pathway*	*Relevance to the Disease*	*Relevance in CKD*	*Reference*
		NFKB1 / NFKB2	Transcription factor for inflammation	Activated during infection → cytokine production	Persistent NF-κB activation → CKD inflammation and fibrosis	
		IL6	Pro-inflammatory cytokine	Elevated during infections → mediates systemic and renal inflammation	Drives CKD progression via chronic inflammation	
		TNF (Tumor Necrosis	Cytokine, apoptosis, inflammation	Induces renal injury during infections	Promotes renal inflammation, fibrosis, and CKD	
		CFH	Complement regulation	Prevents excessive complement activation during infections	Dysregulation → complement-mediated CKD	
		C3	Complement cascade	Mediates pathogen clearance	Overactivation → glomerular injury and CKD	
		HLA Class II	Adaptive immunity, antigen presentation	Determines susceptibility to infection-induced glomerulonephritis	Autoimmune-mediated renal injury → CKD	
		ACE	RAAS, fibrosis	Activated in infection-induced renal stress	Accelerates CKD progression via fibrosis and glomerular injury	
		TGFB1	Fibrosis, ECM regulation	Activated post-infection → tissue remodeling	Major mediator of CKD fibrosis and progression	
8.	Drug-Induced Nephropathy	ACE	RAAS, fibrosis, vascular tone	RAAS activation can exacerbate nephrotoxicity (e.g., NSAIDs, calcineurin inhibitors)	Drives CKD progression via glomerulosclerosis and fibrosis	
		TGFB1	Fibrosis, extracellular matrix	Upregulated in response to drug-induced tubular injury	Central mediator of renal fibrosis and CKD	
		NFKB1 / NFKB2	Transcription factor for inflammation	Activated by nephrotoxic drugs → cytokine production	Chronic activation contributes to CKD inflammation and progression	
		IL6	Pro-inflammatory cytokine	Upregulated in drug-induced tubular injury	Promotes CKD through inflammation	
		TNF	Apoptosis, inflammation	Mediates tubular apoptosis in nephrotoxicity	Promotes CKD-related renal inflammation and fibrosis	
		SLC22A2	Renal tubular drug transporter	Mediates uptake of nephrotoxic drugs like cisplatin	Variants can modulate susceptibility to CKD	
		ABCB1	Drug efflux transporter	Protects tubular cells from drug accumulation	Dysregulation can exacerbate CKD risk in nephrotoxic drug exposure	

Sr. No	*Diseases*	*Genes*	*Function / Pathway*	*Relevance to the Disease*	*Relevance in CKD*	*Reference*
		KIM1 / HAVCR1 Injury	Marker and mediator of tubular injury	Highly upregulated in drug-induced tubular damage	Indicator and contributor to CKD progression	
		CYP3A5 / CYP2C9	Metabolizes nephrotoxic drugs	Polymorphisms alter susceptibility to drug toxicity	Indirectly affects CKD risk via altered drug clearance	
9.	Autoimmune Diseases	HLA Class II (HLA-DR, HLA-DQ, HLA-DQA1, HLA-DQB1)	Antigen presentation, adaptive immunity	Strongly linked to autoimmune diseases (e.g., SLE, RA, T1D)	Autoimmune-mediated glomerular injury → CKD	
		TNFA	Pro-inflammatory cytokine	Central in autoimmune inflammation	Promotes renal inflammation and fibrosis in CKD	
		IL6	Cytokine, inflammation	Elevated in autoimmune conditions	Contributes to CKD progression via chronic inflammation	
		TGFB1	Fibrosis, ECM regulation	Activated in autoimmune tissue injury	Major driver of renal fibrosis and CKD	
		CFH	Complement regulation	Dysregulation linked to autoimmune kidney injury (e.g., atypical HUS, SLE)	Complement-mediated glomerular injury → CKD	
		C3	Complement cascade	Mediates immune complex clearance	Overactivation → glomerular injury → CKD	
		PDCD1	Immune checkpoint, T-cell regulation	Polymorphisms associated with autoimmune susceptibility	Modulates immune-mediated kidney injury	
		FAS / FASL	Apoptosis regulation	Involved in autoimmune tissue damage	Promotes tubular apoptosis contributing to CKD	
		STAT4 / STAT3	Cytokine signalling	Autoimmune disease susceptibility	Mediates inflammation and fibrosis in CKD	
		ACE	RAAS, fibrosis	Indirectly contributes to autoimmune kidney injury via hypertension	Promotes CKD progression via glomerular sclerosis and fibrosis	

Note: For diseases 2-9, in Table II, all the corresponding references have been cited in the list of references: [6] [12] [34] [52] [72] [83] and [85].

Table III: Core Hub Genes in CKD Across All Aetiologies

Sr. No.	*Gene*	*Pathway / Function*	*Why It's Central Across Diseases*	*Reference*
1.	ACE	RAAS regulation, BP control	Shared in diabetes, hypertension, heart failure, PKD, obstruction → drives glomerular hyperfiltration and sclerosis.	Ebrahimi *et al.,* 2025
2.	TGFB1	Fibrosis, ECM deposition	Universal driver of fibrosis in CKD regardless of trigger (immune, metabolic, obstructive, toxic).	Tang *et al.,* 2021
3.	IL6	Pro-inflammatory cytokine	Chronic inflammation in diabetes, HF, autoimmune, infections, GN → accelerates renal injury.	Kreiner *et al.,* 2022
4.	TNFA	Inflammation, apoptosis	Key mediator of tubular and podocyte injury in drug-induced nephropathy, autoimmune CKD, diabetes, HF.	Ramseyer *et al.,* 2013

Sr. No.	*Gene*	*Pathway / Function*	*Why It's Central Across Diseases*	*Reference*
5.	HLA Class II	Antigen presentation	Strongest immune predisposition genes → central to autoimmune CKD, T1D nephropathy, GN.	Dai *et al.,* 2015
6.	CFH / C3	Complement pathway	Critical in GN, autoimmune, infection-related CKD; complement overactivation → glomerular scarring.	Lemaire *et al.,* 2021
7.	NPHS1 / NPHS2	Glomerular filtration barrier integrity	Directly linked to GN and proteinuric CKD progression; podocyte loss is a common pathway.	Koziell *et al.,* 2002
8.	PPARG	Metabolic regulation, anti-fibrotic	Protects against diabetes, drug-induced, obstructive CKD via anti-inflammatory effects.	Ma *et al.,* 2020
9.	KIM1	Tubular injury marker	Expressed in toxin, drug, obstruction, infection, autoimmune CKD → strong indicator of progression.	Su *et al.,* 2017

IV. Integrated Gene Interaction Networks Underpinning Chronic Kidney Disease

The network maps demonstrate the intricate interconnection of genes and molecular pathways involved in chronic kidney disease (CKD), overlaying common mechanisms in varied etiologies like diabetes, hypertension, immune dysregulation, and fibrosis. Core hub genes like *TGFB1, TNF, IL6, PPARG, ACE, CFH*, and *NPHS1/2* appear to be the main molecular drivers, mediating fibrosis, inflammation, immune regulation, and podocyte damage. The interaction range includes anticipated functional relationships (48.44%), physical interactions (14.31%), pathway relationships (12.74%), and gene interactions (11.60%), in addition to co-expression and co-localization networks. Altogether, these observations highlight that CKD develops not due to sole defects but via a complex genetic and molecular environment, where convergence of overlapping pathways contributes to progressive renal damage (Table III) and (Fig. 2).

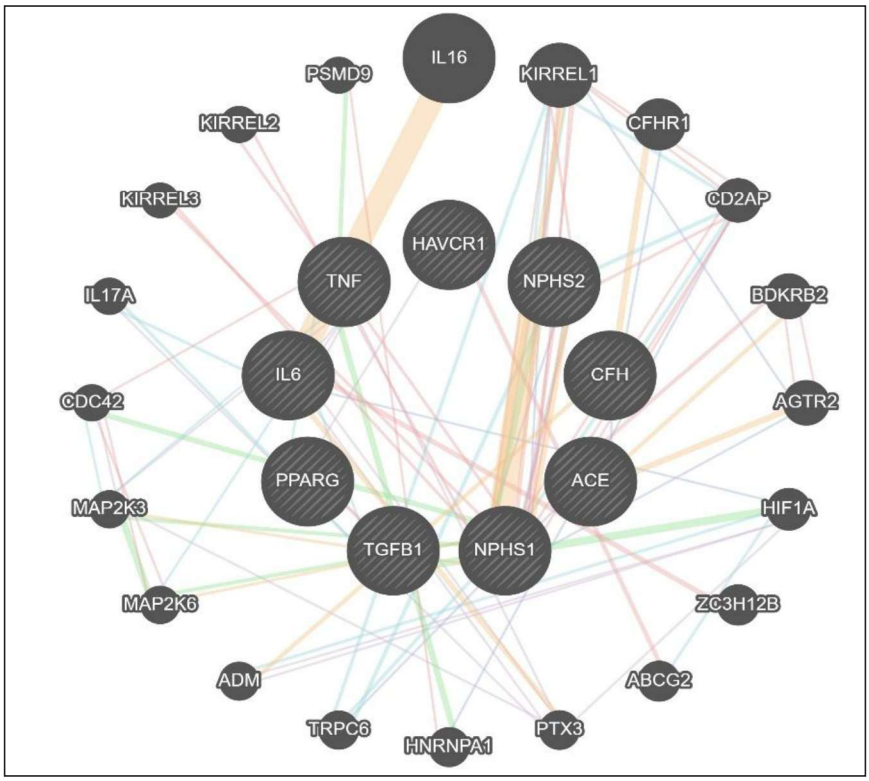

Fig. 2: Core Hub Genes Interaction Network in Chronic Kidney Disease (CKD)

V. Preventive Measures

Chronic kidney disease (CKD) needs medical management by a multi-factorial, evidence-based strategy aimed at slowing progression, minimizing complications, and preventing end-stage renal disease. In diabetic kidney disease (DKD), tight glycemic control is key; HbA1c <7% decreases CKD risk, although higher individualized targets (7.5-8%) are suggested in older or advanced patients to avoid hypoglycemia. Metformin and SGLT2 inhibitors are first-lines for their renal and cardiovascular protective effects, and GLP-1 receptor agonists are second-line useful treatments (Neuen *et al.,* 2019).

- *Blood Pressure Management:* (<130/80 mmHg) is a continued cornerstone, and RAAS blockade (ACE inhibitors or ARBs) decreases proteinuria, intraglomerular pressure, and cardiac risk mandating attention to hyperkalemia and creatinine increase. Lipid control with statins is recommended for all patients with eGFR <60 mL/min/1.73m² or albuminuria, with cardiovascular and moderate renal effects; ezetimibe may be added if LDL lowering is inadequate (Sandhu *et al.,* 2006).
- *Metabolic Acidosis:* This occurs in as many as 19% of patients with advanced CKD, is treated with sodium bicarbonate to keep serum bicarbonate ≥22 mEq/L, with veverimer showing promise as a treatment. Anemia, occurring in >90% of advanced CKD, is caused by decreased erythropoietin and treated with ESAs (epoetin alfa, darbepoetin alfa) when Hb <10 g/dL, but not to Hb >11.5 g/dL in order to avoid increased cardiovascular risk (McMurray *et al.,* 2012).
- *CKD-Mineral and Bone Disorder (CKD-MBD):* This is stimulated by phosphate retention, vitamin D deficiency, and secondary hyperparathyroidism, and treated with restriction of phosphate, calcium-free binders (such as sevelamer), vitamin D supplementation, and calcimimetics for high PTH (McMurray *et al.,* 2012). In general, CKD management combines glycemic, blood pressure, and lipid control with acidosis, anaemia, and mineral imbalance management, with a focus on early, individualized, and closely monitored treatment to maximize renal and cardiovascular outcomes.

VI. Potential Role of Baking Soda in CKD

Sodium bicarbonate ($NaHCO_3$) is an important therapy in chronic kidney disease (CKD) for correcting metabolic acidosis, which arises as kidney function declines and bicarbonate production becomes impaired (blood pH <7.35, serum bicarbonate <22 mEq/L). As a systemic alkalizer, it raises serum bicarbonate, buffers hydrogen ions, and restores acid-base balance, while exerting protective effects by reducing inflammatory mediators (angiotensin II, aldosterone, endothelin-1), promoting nephron adaptation, and restoring α-Klotho, thereby attenuating inflammation-driven renal deterioration (Yang *et al.,* 2024). Clinical evidence supports its efficacy. The de Brito-Ashurst (2009) study demonstrated a slower decline in creatinine clearance and reduced progression to end-stage renal disease. These findings were confirmed by subsequent trials and meta-analyses showing improved serum bicarbonate, slower eGFR decline, modest blood pressure reduction, and an acceptable safety profile. Stage-specific benefits include deceleration of renal failure in stage 4 CKD and improved nutritional status in stage 5 CKD (Table IV). Standard dosing begins at 650 mg twice daily (0.5-1.0 mEq/kg/day), with alternatives such as baking soda preparations or sodium citrate for select patients (Brito *et al.,* 2009).

- *Risks and Monitoring:* Sodium load (~273 mg per gram) can exacerbate hypertension, fluid retention, weight gain, and strain in heart failure. Excess dosing may cause metabolic alkalosis (pH >7.45), leading to respiratory depression, arrhythmias, neurological symptoms, and impaired oxygen delivery; levels >26 mEq/L are linked to higher heart failure risk and mortality. Electrolyte disturbances include hypokalemia, ionized hypocalcemia, and phosphate elevations, while gastrointestinal complications such as bloating, nausea, vomiting, and rarely gastric rupture may occur (Brito *et al.,* 2009). Dosing should be divided, preferably on an empty stomach, targeting serum bicarbonate 22–28 mEq/L without exceeding 26 mEq/L. Monitoring must include serum bicarbonate, electrolytes, blood pressure, arterial blood gases when indicated, and regular assessment of fluid status. Absolute contraindications include metabolic or respiratory alkalosis, hypocalcemia, and severe heart failure with fluid overload, uncontrolled hypertension, and hypersensitivity to bicarbonate. Caution is required in cirrhosis, edematous states, concurrent diuretics, peptic ulcer disease, and advanced CKD. Drug interactions may reduce antihypertensive efficacy, worsen hypokalemia with diuretics, alter cardiac drug responses, or reduce antibiotic absorption (Raphael *et al.,* 2020).

Table IV: Risks and Precautions

Risk	*Explanation*	*References*
High Sodium Load	Increases blood pressure and can worsen heart and kidney function.	(Malta *et al.,* 2018)
Alkalosis	Excess bicarbonate may raise blood pH to dangerous levels.	(Galla *et al.,* 2000)
Electrolyte Imbalance	May alter potassium, calcium, and sodium levels.	(Meng *et al.,* 2022)
Gastrointestinal Issues	Bloating, nausea, gas.	(Iovino *et al.,* 2014)

- *Contraindications: Who Should Avoid Sodium Bicarbonate Therapy*

Sodium bicarbonate therapy is advantageous in CKD patients with established metabolic acidosis but is significant to use with care and contraindications. It must be discontinued in the presence of normal renal function (eGFR >60 mL/min/1.73 m²) because redundant supplementation can result in metabolic alkalosis, electrolyte disturbances (hypokalemia, hypocalcemia), sodium excess, resultant hypertension, fluid overload, and gastrointestinal issues like rupture of the stomach (Brito *et al.,* 2009). Those with uncontrolled hypertension, heart failure, or edematous conditions are especially at risk as usual dosing (0.5-1.0 g three times a day) contributes 400-800 mg sodium daily. Therapy is only recommended if serum bicarbonate is less than 18 mEq/L and should not replace but only add to well-established CKD regimens such as ACE inhibitors or ARBs. Typical dosing is 0.5-1.0 g three times a day or 0.4-1.0 mEq/kg/day, with titration to keep serum bicarbonate at 22–26 mEq/L, not exceeding 28 mEq/L since there is higher risk of heart failure and mortality (Chen *et al.,* 2013). Serum bicarbonate, electrolytes, blood pressure, weight, edema, and clinical symptoms should be intensively monitored, especially during the initial period. Evidence is strongest in stage 4 CKD, reducing kidney function loss, whereas in stage 5, benefits pertain mostly to nutrition. Earlier stages demonstrate little benefit. Caution involves possible drug interactions (e.g., tetracycline, fluoroquinolones, calcium solutions, norepinephrine, dobutamine, amphetamines) and use of pharmaceutical tablets over home baking soda. Where indicated, sodium bicarbonate retards the progression of CKD and enhances prognosis, but therapy needs to be tailored, carefully monitored, and incorporated into global CKD care to reduce cardiovascular, electrolyte, and alkalosis complications (Melamed *et al.,* 2020).

VII. Kidney-Friendly and Alkaline-Reducing Food

Dietary management is the foundation of CKD therapy, focusing on alkaline-forming foods and mineral balance in support of nephroprotection. With deteriorating kidney function (GFR 50–60 mL/min/1.73m²), metabolic acidosis accelerates the course of disease. Alkaline diets that include a high content of fruits and vegetables enhance outcomes, with systematic reviews demonstrating a rise in serum bicarbonate (mean +2.98 mEq/L) and eGFR (mean+3.16 mL/min/1.73m²) (Mahboobi *et al.* 2025). Low-potassium, high-antioxidant fruits like apples, strawberries, and blueberries are great; grapes, watermelon, and papaya are acceptable in moderation, but bananas need careful use in late CKD because of the risk of hyperkalemia. Early CKD (stages 1-2) permits quite liberal fruit consumption with emphasis on alkaline foods; moderate CKD (stages 3-4) necessitates potassium 2,000-4,000 mg/day, phosphorus 800-1,000 mg/day, and protein 0.6-0.8 g/kg/day; advanced CKD (stage 5) mandates tight potassium and phosphorus control, potential fluid restriction, and increased protein (1.0-1.2 g/kg/day) for dialysis patients to avert protein-energy wasting (King and Levey, 1993). Dietary interventions promote fruits, vegetables, and protein sources from plants while balancing acid-forming foods like meat and grains. Portion control advises 2-3 low-potassium fruit servings per day (1 serving = medium fruit or ½ cup berries). Methods such as vegetable leaching will decrease potassium content, although fresh fruit is preferable. With adequate surveillance of serum potassium, phosphorus, and bicarbonate, alkaline diets are safe and effective, providing benefits equal to pharmaceutical bicarbonate therapy without potassium or nutritional adverse effects (Handu *et al.,* 2021).

A. Vegetables, Whole Grains, Legumes and Plant Protein and Healthy Fats

Progressive CKD dietary management focuses on vegetables, whole grains, legumes, and healthy fat with alkaline-forming character and judicious mineral balance in opposition to metabolic acidosis. Low-potassium vegetables including cucumber (147 mg/100g), bottle gourd (87 mg/100g), and ridge gourd (83 mg/100g) are chosen for daily consumption, while moderate-potassium vegetables like cauliflower (299 mg/100g), cabbage (170 mg/100g), and carrot (320 mg/100g) may be added with portion control and potassium-decreasing methods (soaking, boiling, discarding cooking water), which reduce potassium by 10-49% (Mahboobi *et al.,* 2025). Less mineral-rich whole grains like pearled barley (93 mg potassium, 54 mg phosphorus/100g) and white rice (115 mg potassium, 108 mg phosphorus/100g) are safer than quinoa or brown rice; oats must be portioned strictly. Legumes offer vegetarian protein, while moong and masoor dal are best after soaking and boiling (reduces potassium by as much as 80%), but less effective are higher-potassium legumes such as Rajma and chana dal. Canned legumes provide a safer option. Healthy oils like mustard and extra-virgin olive oil promote heart and kidney health, and flaxseed and chia seeds supply plant-based omega-3s in small amounts; avocado and canola oils provide flexibility with high smoke points. Portion control involves ½ cup cooked cereals, ¼ cup legumes, and 1-2 teaspoons of oil per day, along with alkaline vegetables to maximize acid-base balance (Kalantar *et al.,* 2021). Ongoing monitoring of serum phosphorus, potassium, and bicarbonate is necessary, as tolerance differs by CKD stage. Strategic selection, preparation, and portioning enable CKD patients to nourish, manage mineral load, decelerate disease progression, and promote metabolic and renal health.

B. Herbs and Spices

Turmeric, ginger, garlic, coriander, cumin, fennel, and basil are some of the herbs and spices with alkaline-elevating, anti-inflammatory, and digestive benefits that assist the kidneys in CKD when consumed in moderation. Turmeric's bioactive curcumin suppresses body wide inflammation, adjusts intestinal

permeability, and guards against inflammatory damage due to CKD. Ginger has antioxidant and anti-inflammatory properties, decreases renal inflammation, and enhances resistance against edema and infections. Garlic, which is rich in sulphur components such as allicin, decreases proinflammatory markers (e.g., CRP), improves antioxidant defences, and preserves cardiovascular and renal function. Alkaline-forming coriander, cumin, fennel, and basil promote digestion and detoxification, and coriander and fennel serve as a gentle diuretic to enhance clearance through the urine (Table V). For optimal benefit and avoidance of risk, salt-laden or processed spice mixtures should be avoided, as increased sodium may exacerbate hypertension and further advance CKD (Tangkiatkumjai *et al.,* 2015).

Table V: Herbs to Avoid in CKD

Herb	*Reason*	*References*
Aristolochia	Known nephrotoxin; banned in many countries.	(Han *et al.,* 2019)
Aloe vera (oral)	Can cause potassium imbalance.	(Saka *et al.,* 2012)
Licorice (Mulethi)	Causes sodium retention and potassium loss.	(Albahlawan *et al.,* 2024)
Dandelion	Diuretic but may cause potassium disturbance.	(Clare *et al.,* 2009)
Turmeric in excess	High oxalates – problematic if stone-prone.	(Washington *et al.,* 2024)

C. Hydration

Hydration is essential in CKD, using plain water at 1.2-2.0 litres (6-8 glasses) per day unless limited in end-stage or dialysis, helping glomerular filtration and minimizing risk of nephrosclerosis. Traditional beverage sources such as barley water provide mild diuretic and alkalizing effects, and coconut water supplies hydration and electrolytes but must be kept to a minimum with end-stage CKD because of high potassium and hyperkalemia risk. More fluid intake reduces ADH activity and slows cyst growth in polycystic kidney disease. Fresh cooking herbs and spices are safer than concentrated supplements, which can build up or interact with medications in renal failure (Table VI). Fluid and herbal adjustments should be individualized with consideration of CKD stage, comorbid conditions, and laboratory monitoring, preferably under the supervision of a nephrologist or renal dietician (Wagner *et al.,* 2022).

Table VI: Promising and Relatively Safe Herbal Formulations for CKD

Herbal Formulation	*Key Active Compounds*	*Evidence / Clinical Benefits*	*Mechanism of Action*	*Safety Profile*	*Notes*	*Reference*
Punarnava (Boerhavia diffusa)	Punarnavine, Boeravinones A–F, Flavonoids	12% GFR improvement in stage II CKD (12 weeks)	Enhances renal blood flow; reduces oxidative stress; modulates pro-inflammatory cytokines; nephroprotective; punarnavine has immunomodulatory effects.	Generally well-tolerated; mild GI upset; risk of excessive diuresis; requires electrolyte (esp. K^+) monitoring.	Strongest single-herb clinical foundation in CKD. Best for early-moderate stages.	(Souza *et al.,* 2024) (Shankara-narayanan *et al.,* 2023)
Gokshura (Tribulus terrestris)	Steroidal saponins (Protodioscin, Diosgenin)	Reduces creatinine & urea; improves urine output; comparable efficacy to standard therapy for microalbuminuria in diabetes	Diuretic; renal protective; improves kidney architecture in animal models.	Generally safe in traditional use; case reports of nephrotoxicity/ hepatotoxicity at high doses/ prolonged use; caution in concentrated extracts.	Promising, but clinical use must be cautious. Avoid high-dose extracts.	(Kamboj *et al.,* 2011) (Samani *et al.,* 2016) (Najafi *et al.,* 2014)

Herbal Formulation	*Key Active Compounds*	*Evidence / Clinical Benefits*	*Mechanism of Action*	*Safety Profile*	*Notes*	*Reference*
Varun (Crataeva nurvala)	Alkaloids, Triterpenes, Flavonoids	Reduces kidney stone formation (55.55% - 22.22% in treated groups); effective in obstructive nephropathy	Increases urine volume; acidifies urine pH; prevents Ca-phosphate precipitation; anti-aggregation action prevents crystallization.	Generally well-tolerated; long-term safety data limited.	Best for stone prevention/ obstructive nephropathy rather than direct CKD slowing.	(Agarwal *et al.,* 2010) (Kaushik *et al.,* 2021)
Chandraprabha Vati (37-herb classical formulation)	Shilajit, Guggulu, Punarnava, others	Observed benefits for UTI, fluid retention, and kidney stone prevention	Multifactorial due to 37 ingredients (diuretic, anti-inflammatory, antimicrobial, nephroprotective).	Caution: risk of herb–drug interactions; not suitable for advanced CKD, severe liver disease, or uncontrolled hypertension.	Traditional formulation; modern evidence limited; should only be used under supervision.	(Jagani *et al.,* 2022) (Weerasekera *et al.,* 2015)
Neeri KFT (polyherbal commercial formulation)	Standardized extracts: Punarnava, Gokshura, Varuna, Haridra, others	Multiple trials: ↓ serum creatinine, urea, uric acid; improved energy; stabilized creatinine; delayed CKD progression; possibly ↓ dialysis need	Synergistic nephroprotective, antioxidant, and anti-inflammatory effects from multiple standardized herbs.	Good tolerability in clinical trials; limited data on long-term safety.	Strongest clinical evidence among commercial products; promising adjunct therapy.	(Gautam *et al.,* 2021) (Gaurav *et al.,* 2023)

VIII. Conclusion

Remedies rooted in herbal and dietary traditions have always offered healing to humanity, and their role in chronic kidney disease (CKD) management is no exception. While CKD remains a complex, multifactorial disorder driven by diverse aetiologies such as diabetes, hypertension, and infections, a growing body of evidence supports the value of nephroprotective foods, fruits, and herbal supplements with antioxidative and anti-inflammatory potential. When combined with early detection, lifestyle modification, and optimized pharmacological therapies, these natural interventions provide a multidimensional strategy to delay disease progression and preserve kidney function. Integrating such holistic approaches into CKD care not only broadens therapeutic options but also underscores the importance of aligning modern medicine with the healing resources nature continues to offer.

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