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Chronic Kidney Disease: Bridging Conventional Therapeutics and Emerging Molecular Innovations

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Abstract: Chronic kidney disease (CKD) is a significant public health issue worldwide, contributing to a growing burden on healthcare systems and global economies. While conventional management strategies emphasize early detection, prevention, and addressing underlying causes to slow disease progression, CKD is frequently asymptomatic in its early stages. This often results in delayed diagnosis and initiation of treatment only at advanced stages, when therapeutic options are limited and less effective. The shortcomings of current approaches highlight the need for strategies to mitigate disease progression and restore renal function, particularly during the early phases of the disease. This review explores both established and emerging strategies for the effective management of CKD. It begins by examining the etiology and risk factors that contribute to disease onset and progression, followed by a detailed discussion of conventional interventions including lifestyle and dietary modifications, pharmacological treatments, dialysis and kidney transplantation. Additionally, novel therapeutic approaches such as antifibrotic agents, new renin-angiotensin-aldosterone system (RAAS) modulators, stem cell therapy, precision medicine, novel biomarkers, and the role of gut–kidney axis, which show promise in enhancing clinical outcomes are discussed. By identifying the existing challenges and outlining future directions, this review aims to encourage the development of more individualized, proactive, and effective treatment strategies. All in all, it serves as a valuable resource for clinicians and researchers working toward improving early intervention and long-term outcomes for patients at risk of or living with CKD.

Keywords: chronic kidney disease; risk factors; management strategies; emerging therapeutic; molecular therapies

1. Introduction

Chronic kidney disease (CKD) is a clinical condition characterized by the progressive and irreversible loss of kidney function, defined by a sustained estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 for 3 months or more, irrespective of the cause[1]. The disease progression is primarily driven by glomerulosclerosis and tubulointerstitial fibrosis. Key pathological mechanisms involving podocyte injury, mesangial expansion, and fibroblast activation. These lead to excessive extracellular matrix (ECM) deposition, tissue scarring and disrupted renal structure, resulting in active urinary sediments, proteinuria or impaired excretory capacity[2,3]. Across its various stages, CKD is often associated with an elevated risk of cardiovascular disease (CVD)[4], hospitalizations[5], cognitive impairment[6], and all-cause mortality[7].

CKD is a long-standing global public health concern, affecting approximately 10–15% of the world's population[8]. To date, it is estimated that approximately 850 million people worldwide are affected by kidney disease, with the majority residing in low- and lower-middle-income countries, as many of these individuals lack adequate access to screening, preventive care or treatment services[9,10]. From 1990 to 2016, the global incidence of CKD increased by 89%, prevalence by 87%, and CKD-related disability-adjusted life years (DALYs) by 62%[11]. The global mortality from all kidney diseases is estimated to range between 5 million and 11 million deaths per year[12]. CKD-related mortality has shown a consistent upward trend across all age groups and genders from 1990 to 2021[13], with a notable 50% increase in deaths observed from 2000 to 2019[14]. Other than urbanization and industrialization, the growing global prevalence of CKD is partly attributed to the aging population, as elderly populations are more susceptible to kidney dysfunction[15]. Consequently, CKD continues to impose a substantial and escalating burden on healthcare systems and global economies[16,17].

This concerning trend is also evident in Malaysia[18]. The prevalence of CKD increased from 13,479 per million population in 2004 to 20,589 per million in 2008[19]. Although a nationwide prevalence is yet to be definitively established, the estimated incidence of CKD in West Malaysia is approximately 9.07%. Stage-wise distribution includes 4.16% (Stage 1), 2.05% (Stage 2), 2.26% (Stage 3), 0.24% (Stage 4), and 0.36% (Stage 5)[20]. According to the 22nd report of the Malaysian Dialysis and Transplant Registry, the number of patients on dialysis grew significantly from 13,356 in 2004 to 34,767 in 2014[21]. These statistics highlight the growing burden of CKD within Malaysia and emphasize the urgent need for early detection strategies and enhanced renal care infrastructure to prevent disease progression.

Conventional management strategies for CKD emphasize early detection, prevention and addressing the underlying cause to slow disease progression[22,23]. However, the disease is often asymptomatic in its early stages, and commonly used diagnostic tools lack the sensitivity to detect early renal impairment[9]. Therefore, many patients are diagnosed only in the advanced stages, when therapeutic options are more constrained and less effective.

Although pharmacological agents such as sodium-glucose cotransporter-2 (SGLT2) inhibitors[24], renin-angiotensin-aldosterone system (RAAS)[25] and nonsteroidal mineralocorticoid receptor antagonists (nsMRAs)[26] have demonstrated clinical efficacy, their integration into routine practice remains limited due to under recognition of their benefits, insufficient clinician familiarity and concerns about adverse effects[27]. These challenges underscore the urgent need for more effective therapeutic strategies that not only mitigate disease progression but also potentially restore kidney function, especially in the early stages of CKD[28].

This review provides a comprehensive overview of CKD management, expanding from conventional approaches to cutting-edge molecular strategies. It covers the etiology and risk factors that drive the onset and progression of CKD, and critically evaluates the conventional management approaches, including lifestyle and dietary modifications, pharmacological therapies, dialysis modalities and kidney transplantation. Importantly, the review delves into emerging therapeutic strategies, including antifibrotic agents, new RAAS modulators, stem cell-based therapies, precision medicine approaches, novel diagnostic and prognostic biomarkers, and the role of gut-kidney axis, aimed at addressing the underlying molecular and cellular mechanisms of CKD. The underlying mechanism of action, therapeutic potential and implementation challenges of each strategy are discussed. By integrating insights across traditional and novel domains, this review identifies existing gaps in care and outlines future directions, ultimately supporting the development of earlier, more individualized, and mechanistically targeted treatment paradigms for patients at risk of or living with CKD.

2. Etiology and Risk Factors of CKD

The onset and progression of CKD are influenced by a wide range of etiological factors and risk determinants. These include non-modifiable factors such as age and gender disparities, along with hereditary disorders, as well as modifiable contributors like glomerulonephritis, non-communicable diseases (NCDs), environmental exposures, and lifestyle-related behaviors[29,30]. Figure 1 provides a visual summary of the various etiologies and risk factors associated with CKD, which are further elaborated in the subsequent subsections.

2.1. Age and Gender Disparities

Older individuals face a higher risk of CKD due to accelerated whole-body systemic aging and chronic inflammation[14,31]. They are also more prone to complications and possess higher mortality rate compared to younger patients. Age-related disparities are evident in later disease stages, with older adults less likely to receive kidney transplantation and having poorer recovery outcomes[14].

Gender differences are also prominent as men generally have higher risks of developing CKD due to lifestyle factors such as smoking, binge alcohol consumption, dietary practices, excessive injuries and occupational exposure[31,32]. Despite men being more likely to receive treatment such as dialysis or transplantation, women with CKD often report lower quality of life, potentially due to differences in physical and mental health. Regardless of gender, CKD eventually adversely impacts the mental health of 30 to 50% of family members and caregivers, developing anxiety and/or depression[14].

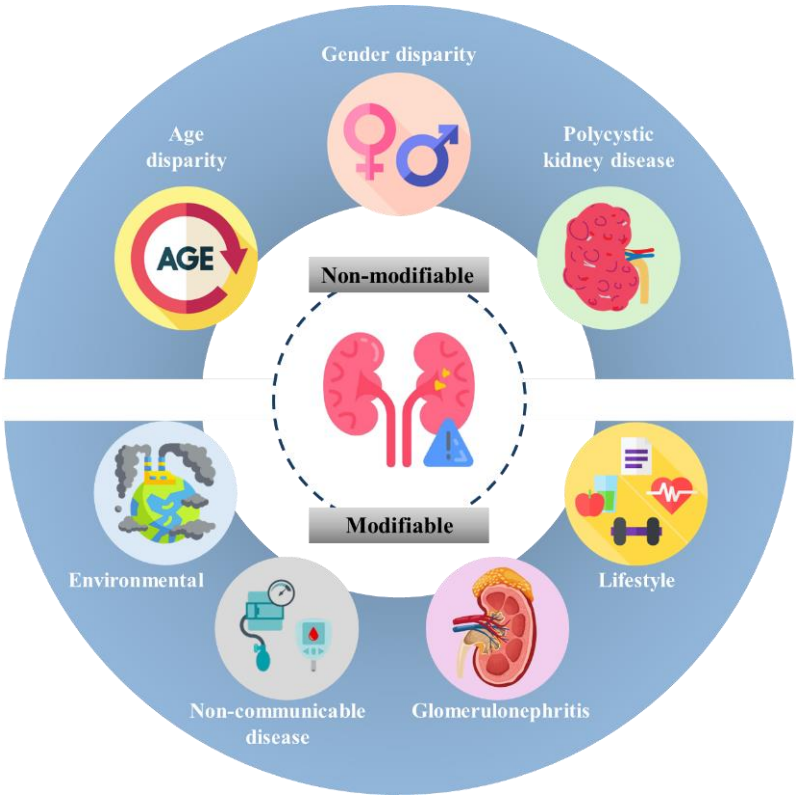

Figure 1. Etiology and risks factors of CKD. The figure was created using Microsoft® PowerPoint® for Microsoft 365 MSO (Version 2507 Build 16.0.19029.20136).

2.2. Polycystic Kidney Disease

Polycystic kidney disease is known as the hereditary CKD that is characterized by the presented of large, fluid-filled cysts within the kidney[33]. Cysts can also be found in other organs such as liver and spleen[31]. The formation of kidney cyst could be related to hyperplasia of the tubular epithelium, which causes partial blockage of the tubules that prevent urine flow[34]. The obstruction can potentially cause urinary tract infection and oliguria. Patients with polycystic kidney disease prognosis may also present with extrarenal symptoms such as secondary hypertension, cerebral aneurysms, cardiac valvular abnormalities and cardiovascular complications[31,35]. Polycystic kidney disease is a genetic disorder commonly inherited across generations. The inheritance of polycystic kidney

disease occurs in two forms which are autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD)[35]. ADPKD is the common form of the polycystic kidney disease compared to ARPKD. ADPKD is developed from either polycystin-1 or polycystin-2 gene mutation, which characterized as an adult-onset multisystem, progressive disorder. Meanwhile, ARPKD is developed from PKHD1 gene mutation that encodes for fibrocystin, which usually diagnosed on infants, baby or children.

2.3. Glomerulonephritis

Glomerulonephritis causes inflammation and damage of glomerular capillaries, tubulointerstitium and tubuli, affecting waste filtering function from the blood[36]. It will trigger the release of pro-inflammatory cytokines and chemokines into the surrounding of kidney to build crescents, which composed of proliferating epithelial cells and infiltrating immune cells[37]. The formation of crescents in Bowman's capsule can develop into different diseases such as systemic lupus erythematosus, haematuria, proteinuria, vasculitis or rapidly progressive glomerulonephritis, and eventually could lead to kidney failure or death in the end stage[31,37,38]. Glomerulonephritis is also associated with lupus, hypertension and diabetes mellitus, that cause inflammation to the kidney tissues[38,39]. Elderly patients may possess higher risk of developing glomerulonephritis due to the increased prevalence of metabolic syndromes, such as hypertension, diabetes and dyslipidemia, that are closely linked to age-related immune dysfunction and chronic inflammation[40]. Patients who developed glomerulonephritis also have high risk in developing CVD that led to mortality in the later stage of glomerulonephritis[39].

2.4. Non-Communicable Diseases

Despite there being no noticeable clinical symptoms in the early stage of CKD, patients with NCDs, such as hypertension and diabetes mellitus could be the initiations of the early stages of CKD. According to earlier studies[31,41], there was approximately 40 to 60% of hypertension and diabetic mellitus patients develop CKD. Without proper management, this can lead to decreased estimated glomerular filtration rate and increased albuminuria in the later stage of CKD[42]. This is because both high blood pressure and blood sugar level can narrow blood vessels and damage kidney cells, leading to impair glomerular filtration by damaging glomeruli and interstitium in the high osmotic pressure kidney environment. Further stress from hypertension and diabetes mellitus also stimulates sympathetic nervous system and elevate cytokines level to induce inflammation[32].

Other NCD complications such as dyslipidaemia and CVD can occur in any stage of CKD, which can directly lead to mortality before reaching kidney and renal failure[32,42]. CKD will disturb lipid metabolism, leading to elevation of triglycerides and contributing to atherosclerosis, one of the major causes of CVD. Moreover, CKD has recently been found to increase the risk of developing severe infections such as tuberculosis and COVID-19[14]. The increased risk of severe infections in CKD patients is believed to resulted from the deposition of uraemic toxin and inflammation triggered extensive interaction between kidneys and other organs. These interactions contribute to a higher burden of comorbidity, which is the presence of additional health conditions that coexist with CKD, such as cardiovascular and infectious diseases, ultimately worsening patient outcomes[14]. Therefore, regulation of NCDs and severe infection is critical to reduce the risk of developing NCD complications other than preventing CKD progression to end-stage kidney diseases.

2.5. Environmental and Lifestyle Factors

Environmental and lifestyle factors play a critical role in the development and progression of CKD. The high prevalence of CKD in certain populations is closely linked to environmental and lifestyle factors compounded by poor resource settings. In many developing regions such as Southern Asia and Sub-Saharan Africa, exposure to contaminated water, use of nephrotoxic herbal remedies, environmental pollutants and physically demanding labour without adequate protection contribute to kidney damage. These risks are further exacerbated by limited health education, poor access to clean living conditions, and inadequate healthcare infrastructure. Individuals in these regions often remain unaware of CKD, with over 90% lacking disease awareness[14], despite spending 2 to 3% of their annual health expenditure on renal therapies[43]. These environmental exposures, combined with poverty and limited education, create conditions that heighten vulnerability to CKD and hinder early diagnosis and prevention.

Global warming and exposure to environmental toxins have been shown to increase physical stress, particularly among agricultural and outdoor workers, thereby heightening their risk of kidney damage[14]. Additionally, prenatal and early-life exposures contribute significantly to CKD risk. Malnutrition and toxic environmental exposure during pregnancy can predispose newborns to proteinuria, hypertension, and ultimately CKD later in life[14]. Unhealthy lifestyle behaviors are also strongly associated with increased CKD risk. Kelly *et al*.[43] and Alkhatib *et al*.[32] discussed several unhealthy lifestyle practices, including high alcohol consumption, smoking, lack of physical activity and unhealthy dietary practice. Binge drinking can lead to albuminuria and direct kidney injury[44], while smoking promotes

insulin resistance, vascular permeability, and albuminuria, all of which can progress to cardiovascular complications in CKD. Sedentary lifestyles are linked to obesity, diabetes, and cardiovascular disease, key contributors to CKD. Furthermore, diets high in sugar, salt, saturated fat, and protein, and low in fibre, fruits, vegetables, and unsaturated fats, have been recognized as major dietary risk factors for CKD development.

3. Conventional CKD Management Strategies

Numerous conventional strategies have long been employed in the management of CKD, including dietary and lifestyle modifications, pharmacological interventions, renal replacement therapy and kidney transplantation[45,46]. These approaches, illustrated in Figure 2, mainly aim to slow disease progression, manage complications, and improve patient outcomes.

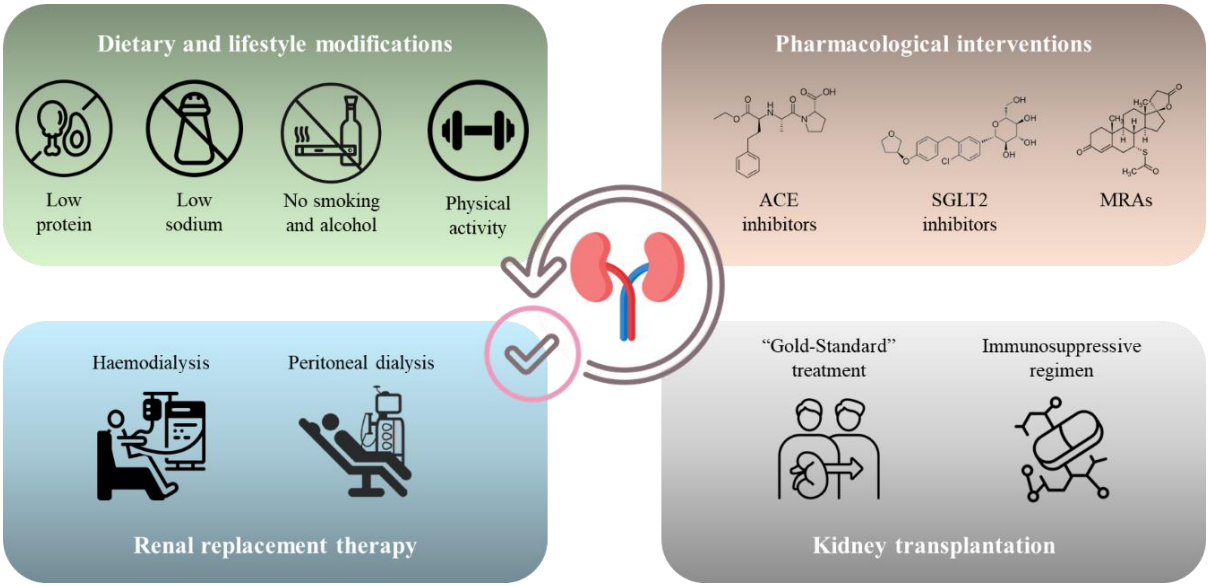

Figure 2. CKD management strategies. The figure was created using Microsoft® PowerPoint® for Microsoft 365 MSO (Version 2507 Build 16.0.19029.20136).

3.1. Dietary and Lifestyle Modifications

Protein intake reduction is the most common dietary strategy introduced to CKD patients to reduce intraglomerular hypertension, kidney hyperfiltration, glomerular injury and proteinuria[32,47]. By introducing low protein diet to CKD patients, it was effective in reducing serum urea, serum uric acid, endogenous acid production and potential renal acid load at least 50 % after 6 months. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) also reported that low-protein diet can slow the progression of late-stage renal disease and improve the quality of life in CKD patients[32].

Additionally, reduction of salt intake also significantly alleviates CKD patient's condition. It is known that lowering salt intake is the most common dietary practice to keep NCDs away from individual. Other than regulating both blood pressure and flow, a low salt diet can reduce glomerular pressure, lowering proteinuria and serum creatinine content[32]. It also reduces the risk of developing CVD in the later stage of CKD.

Mediterranean diet is one of the well-known dietary patterns available in worldwide that is suitable and recommended to CKD patients. It is known for high intake of plant-based food, healthy fats products and moderate amounts of lean protein food, where the protein intake can be modified in accordance with patient conditions[42]. Mediterranean diet is effective to control daily calories, sodium, potassium, phosphate, calcium and protein intake. The adherence to Mediterranean diet does not only aids in reducing the decline of renal function, it also benefits healthy individuals on reducing the risk of developing CKD in the future[42].

Aside from diet modification, lifestyle changes can be done to reduce the risk of gaining CKD. The changes can be carried out through reduction of alcohol consumption, avoid smoking and increase physical activity[32,43]. There are two highlights that need to be mentioned on reduction of alcohol consumption and avoid smoking, respectively. Reduction of alcohol from heavy drinker to moderate drinker was in line with public health guidelines and associated with lower occurrence of CKD; Avoid smoking by former smoker may not be effective on developing CKD, where it shared similar risk with current smoker when compared to individuals that never smoke[43].

3.2. Pharmacological Interventions

RAAS inhibitors are considered the first-line pharmacological agents for preventing and slowing the progression of CKD[48]. Among them, angiotensin-converting enzyme (ACE) inhibitors are widely recognized for their effectiveness in managing proteinuria and delaying the advancement of CKD to end-stage renal disease. Besides that, it is also used to treat CKD patients suffering from hypertension, diabetes mellitus and albuminuria[42]. The regulation of hypertension and diabetes mellitus by ACE inhibitor lowers the risk of gaining CVD and reduces the rate of mortality from both CKD and cardiovascular events[32]. ACE inhibitors have also been reported to use as the most important drug intervention to control hypertension that eventually slow down the progression of CKD[31].

SGLT2 inhibitors are mainly used on the CKD patient who is associated with diabetes mellitus[32]. In addition to reducing glucose reabsorption from the renal tubules into the

bloodstream, SGLT2 inhibitors exhibit renoprotective effects similar to those of ACE inhibitors, including the reduction of albuminuria and lowering the risk of CVD and advancement of CKD[32,42]. The therapeutic mechanisms of SGLT2 inhibitors extend beyond glycemic control and involve modulation of the RAAS, elevation of hematocrit levels, shifts in energy substrate utilization, and attenuation of systemic inflammation and oxidative stress.

Moreover, mineralocorticoid receptor antagonists (MRAs) are a class of medications that block the effects of aldosterone, a hormone that regulates sodium and water balance in the body. MRAs, including spironolactone and eplerenone, have demonstrated benefits in CKD by reducing renal inflammation, oxidative stress, and fibrosis[49]. Despite their therapeutic potential, the clinical use of MRAs in CKD has been limited due to the risk of hyperkalemia, particularly in patients with advanced renal dysfunction or when used concurrently with other RAAS inhibitors. As potassium-sparing diuretics, MRAs can elevate serum potassium levels, posing a safety concern in susceptible populations[50].

Other pharmacological interventions to CKD patients such as phosphate binders, loop diuretic, statin and iron deficiency have been recommended by Japanese Society of Nephrology[51]. Phosphate binders or non-calcium containing phosphate binders are given to CKD patients with hyperphosphatemia to reduce mortality progression and prevent vascular calcification progression[52]; loop diuretic is usually prescribed to diabetic kidney disease to treat edema and reduce blood pressure[53]; statin is given to CKD patients with dyslipidemia to reduce the risk of CVD besides reduce urinary protein excretion and delay renal dysfunction[54]; Lastly, for CKD patient who are suffering anaemia, iron supplementation is recommended especially for those who with iron deficiency[55].

3.3. Renal Replacement Therapy

Haemodialysis and peritoneal dialysis are the common renal replacement therapy introduced to patients with end-stage renal diseases to remove waste products, electrolytes and excess fluid from the bloodstream[56]. Peritoneal dialysis is a type of dialysis that introduces dialysate into abdominal cavity that as a filter to remove waste and excess fluid from the blood. Haemodialysis, on the other hand, uses an artificial kidney machine (dialyzer) to filter waste products, excess fluids, and electrolytes from the blood before returning the cleaned blood to the body.

Peritoneal dialysis offers numerous advantages over haemodialysis. It is cost-effective, high feasibility, has better preservation of residual kidney function, improve quality of life and reduce both exposure and risk to hospital-acquired infections[57,58].

Ngamvichchukorn *et al*.[59] found that peritoneal dialysis can reduce the risk of delayed graft function after kidney transplantation. Unlike haemodialysis, several complications can occur on patient such as fatigue, bone & joint pain, drowsiness, insomnia, anxiety, sexual dysfunction, muscle cramps, gastrointestinal distress, dyspnoea, itching, heartburn or edema. In addition, haemodialysis may not be suitable for countries to have long exposure to extreme climate change, events and disasters such as drought, earthquake, flood, snowstorm and war due to difficulty accessing haemodialysis facilities[14]. In fact, nearly 50–90% of haemodialysis patients experience chronic kidney disease-associated pruritus (CKD-aP), a debilitating condition that significantly impairs quality of life[8]. CKD-aP significantly reduces quality of life and further impairs patients' mental and physical well-being, contributing to fatigue, depression, and disrupted sleep patterns[60].

Despite peritoneal dialysis having so many advantages than haemodialysis, nearly 90% of worldwide patients preferred haemodialysis compared to peritoneal dialysis[61]. This is because haemodialysis is conducted by professional healthcare that can reduce patient self-error, mistake and burden during peritoneal dialysis[62], including the storage of peritoneal dialysis fluid. Haemodialysis also required least sessions and least interference with daily activities when compared to peritoneal dialysis[58]. Lastly, haemodialysis offers better blood pressure control & mineral balance during the waste-removal process from the patient blood.

3.4. Kidney Transplantation

Kidney transplantation is known as "Gold-Standard" treatment for patients with end-stage renal disease to provides better quality of life and more sustainable than both peritoneal dialysis and haemodialysis[57]. According to Francis *et al*.[14], the number of patients to receive kidney transplantation will increase to 5.4 million by 2030, where Africa has the highest number of patients among the global.

Kidney transplant immunosuppression will be given to the kidney recipients after completing the transplantation. This is to prevent the recipient's immune system from attacking the transplanted kidney. It is reported that 90% of the patients will receive calcineurin inhibitor–based immunosuppressive regimen with tacrolimus and mycophenolate, either with or without steroid[63]. This treatment was found to be effective in prevent acute rejection and superior glomerular filtration rate in 1 to 3 years[64]. However, kidney recipients may also experience prolonged catheterization, urinary leakage and severe vesicoureteral reflux due to decreased bladder capacity, detrusor over-activity and impaired bladder emptying during CKD[57].

Despite kidney transplantation is the "Gold-Standard" treatment for patients with end-stage renal disease, most of the patients do not able to receive a kidney transplant on time. This is because of lack of suitable kidney donors, late referral to nephrology unit and financial burden[57,59]. Kidney rejection may also occur after a successful operation, and it possesses higher risk of mortality than the beginning of renal therapy. The main sign of kidney rejection is delayed graft function, which is indicated by immediate dialysis treatment after a week of transplantation or a decrease of serum creatinine to 50% or below after 3 days of transplantation. Hence, it is important to know that preserving graft function and better residual renal function is vital for long-term patient survival before undergo kidney transplantation[57].

There are some factors to be considered to improve the kidney transplantation outcome. Kidney transplantation within same gender has higher acceptability and lower risk of early graft loss as compared to different genders. The age of donor is also an important consideration, which kidney transplantation from very young or very old donor has high risk of poor transplantation. Older patients are suggested to receive kidney transplantation from older donors, which the kidney could have lower allograft survival period. Lastly, the patient who receive the kidney transplantation from a living donor has longer-term of morbidity and mortality compared to deceased donor. However, living donors with hypertension and diabetes mellitus are disqualified from being a kidney donor to the patients[63].

4. Emerging Therapies for CKD

Conventional approaches for the treatment of CKD pose limitations, particularly at molecular level. As nephrology advances, there is growing interest in precision medicine, regenerative therapies, and artificial intelligence (AI)-driven prediction models to personalise treatment and improve patient outcomes. Various emerging therapies have been developed to enhance renal preservation, mitigate disease progression, and improve long-term outcomes for CKD patients.

4.1. Antifibrotic Agents

Fibrosis is a major driver of CKD progression, characterised by excessive ECM accumulation due to a dysregulated wound-healing response following chronic or severe tissue damage[65]. Renal fibrosis, which includes tubulointerstitial fibrosis, glomerulosclerosis, and vascular fibrosis, represents the final pathological stage of various CKD types, regardless of their underlying causes[66]. Despite the widespread use of conventional therapies, such as RAAS inhibitors and SGLT2 inhibitors, their efficacy in

halting fibrosis remains limited. This has prompted the exploration of targeted anti-fibrotic agents that can modulate disease mechanisms at the cellular level. A number of promising candidates have been identified (Table 1), many of which are designed to interfere with signalling cascades involved in ECM production, fibroblast activation, and inflammation, offering new avenues for slowing or potentially reversing CKD progression.

Table 1. Potential antifibrotic therapies for CKD

Antifibrotic therapy	Mechanism of action	Clinical status	Efficacy in CKD	References
Pentoxifylline	Non-selective phosphodiesterase (PDE) inhibitor; increases cyclic adenosine monophosphate (cAMP) levels, reducing inflammatory cytokines (TNF-α, IL-6, CRP) and fibrosis-associated molecules (TGF-β, Smad3/4, CTGF, collagen)	Investigated in multiple clinical trials; shown to reduce proteinuria and inflammatory markers	Slows CKD progression, stabilizes renal function, enhances soluble Klotho levels, may reduce cardiovascular mortality	[67–70]
Pirfenidone	Inhibits TGF-β1 and fibrogenic pathways; suppresses inflammatory cytokine expression (TNF-α), modulates ECM deposition	Preclinical studies in CKD; approved for idiopathic pulmonary fibrosis (IPF)	Demonstrated fibrosis reduction in animal models; potential renoprotective effects but requires further validation	[71–73]
Lademirsen (SAR339375)	Antagomir targeting microRNA-21 (miR-21), reducing fibroblast activation, ECM accumulation, and inflammatory cytokines	Phase 2 clinical trials in Alport Syndrome terminated due to futility	Showed renal fibrosis marker reduction in preclinical models; lacked significant eGFR improvement in human trials	[73–76]
Nintedanib	Tyrosine kinase inhibitors targeting PDGFR, FGFR, VEGFR, and other fibrosis-associated pathways; suppresses fibroblast proliferation and ECM accumulation	Approved for pulmonary fibrosis and some interstitial lung diseases; emerging research in CKD	Demonstrated efficacy in reducing cyst growth and fibrosis in ADPKD models; potential application in CKD remains under investigation	[77–79]

4.1.1. Pentoxifylline

Pentoxifylline, a non-selective phosphodiesterase (PDE) inhibitor, exhibits anti-inflammatory, anti-proliferative and anti-fibrotic properties, making it a promising adjunct therapy for CKD[67]. Originally developed to improve microcirculation in patients with intermittent claudication due to peripheral vascular disease[80], it has been since repurposed for various fibrotic conditions, such as osteoradionecrosis, alcoholic hepatitis, oral submucous fibrosis and etc. which include renal fibrosis[81–85]. Its mechanism of action of pentoxifylline revolves around PDE inhibition, leading to increased cyclic adenosine monophosphate (cAMP) levels, which modulates inflammatory cytokine production[67]. Pentoxifylline has been shown to reduce tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), key mediators of CKD progression[67], while attenuating renal fibrosis by inhibiting cytokines (TNF-α, nuclear factor-κB, intercellular adhesion molecule-1, MCP-1 and CX3CL1/fractalkine), mitogens (platelet-derived growth factor, mitogen-activated protein kinase, phosphatidylinositol 3-kinase, Akt/protein kinase B and cyclin D1) and fibrogenic molecules (transforming growth factor-β, Smad3/4, connective tissue growth factor, collagen types 1 & 3, fibronectin and α-smooth muscle actin)[86–88]. Clinically, pentoxifylline has demonstrated renoprotective effect, reducing proteinuria and stabilising renal function, particularly when used in combination with RAAS blockade[67]. A randomised clinical trial, reported slowed decline of glomerular filtration rate (GFR) and improved inflammatory markers, reinforcing its nephroprotective potential[69]. Additionally, it enhances soluble Klotho levels, a crucial protein linked to longevity and kidney health[70]. Beyond its renal benefits, emerging data suggest that pentoxifylline reduces cardiovascular mortality, a major concern in CKD patients[68].

4.1.2. Pirfenidone

Pirfenidone, originally developed for idiopathic pulmonary fibrosis, has demonstrated significant antifibrotic effects in preclinical studies, cell cultures, and in-vivo models of kidney disease. Its mechanism of action involves the inhibition of transforming growth factor-beta (TGF- β1) and other fibrogenic mediators, thereby reducing renal fibrosis[73]. Beyond its antifibrotic effects, pirfenidone also exhibits anti-inflammatory properties, including the suppression of tumour necrosis factor (TNF) expression, further contributing to renal protection[89]. Studies in multiple animal models have demonstrated its ability to mitigate both inflammation, and fibrosis in CKD progression[71]. Additionally, system biology analyses suggest that pirfenidone induces significant alterations in protein and

metabolites profiles, likely mediated through changes in messenger RNA processing regulation, which may further support its therapeutic efficacy[72].

4.1.3. Lademirsen

Lademirsen (SAR339375) is an antagomir which targets microRNA-21 (miR-21), a regulatory RNA molecule that is strongly linked to fibrosis and inflammation in CKD[73]. miR-21 is known to be overexpressed in kidney disease, contributing to fibroblast activation and extracellular matrix accumulation. By silencing miR-21, Lademirsen reduces fibrotic signalling, suppresses inflammatory cytokines such as tumour necrosis factor (TNF-α), and it has shown to preserve nephron integrity in Alport mice[76]. Preclinical studies have shown promising results, with reductions in renal fibrosis markers and improved renal function[74]. However, phase 2 clinical trials in evaluating Lademirsen in Alport Syndrome did not demonstrate significant improvement in estimated glomerular filtration rate (eGFR) decline compared to placebo, leading to trial termination due to futility[75]. Despite these setbacks, miR-21 inhibition remains an intriguing therapeutic avenue, particularly when combined with other antifibrotic or anti-inflammatory strategies to enhance efficacy.

4.1.4. Nintedanib

Nintedanib is a tyrosine kinase inhibitor that primarily targets platelet-derived growth factor receptors (PDGFRs) α and β, fibroblast growth factor receptors (FGFRs) 1-3, vascular endothelial growth receptors (VEGFRs) 1-3, colony-stimulating factor 1 receptor (CSF1R), Fms-like tyrosine kinase-3 (FLT-3), and Lck, Lyn, and Src kinases[77]. These receptors are key drivers of fibrosis, promoting fibroblast activation and extracellular matrix accumulation, which are the hallmarks of CKD progression[79]. By inhibiting these pathways, nintedanib effectively reduces fibroblast proliferation, inflammation, and excessive collagen deposition, thereby limiting renal fibrosis. Moreover, studies indicate that it downregulates extracellular signal-regulated kinase (ERK), protein kinase B (AKT), signal transducer and activator of transcription 3 (STAT3), and mechanistic target of rapamycin (mTOR) signalling, which further suppresses fibrotic progression[78]. While nintedanib is currently approved for idiopathic pulmonary fibrosis (IPF), interstitial lung disease associated with systemic sclerosis, and chronic fibrosing interstitial lung diseases and non-small cell lung carcinoma, recent research has explored its potential benefits in CKD, particularly in autosomal-dominant polycystic kidney disease (ADPKD). In Pkd1RC/RC rat models, nintedanib has been shown to reduce cyst growth, lower kidney-to-body weight ratio, and decrease renal fibrosis, suggesting a possible therapeutic avenue for CKD patients[78].

4.2. New RAAS Modulators

Another major approach in CKD management focuses on optimizing RAAS modulation. The RAAS system plays a pivotal role in CKD progression, with conventional RAAS inhibitors already forming the backbone of treatment. However, limitations such as incomplete blockade and aldosterone escape have driven the development of newer agents that target distinct components of the pathway. These novel RAAS modulators provide refined strategies aimed at enhancing renal protection and delaying disease progression. Various new RAAS modulators for CKD management are summarized in Table 2.

Table 2. Potential new RAAS modulators for CKD

RAAS modulator	Mechanism of action	Clinical status	Efficacy in CKD	References
Direct renin inhibitors (DRIs)	Inhibits renin activity, reducing angiotensin II formation and RAAS activation	Evaluated in non-diabetic CKD; concerns over hyperkalemia and hypotension	Reduces proteinuria; mixed findings on eGFR preservation	[90–92]
Aldosterone synthase inhibitors (ASIs)	Inhibit CYP11B2, blocking aldosterone synthesis and preventing sodium retention	Phase II/III trials for hypertension and CKD ongoing	Lowers BP, attenuates renal fibrosis, potential nephroprotective effects	[93–95]
Endothelin receptor antagonists (ERAs)	Block endothelin-1 (ET-1) signaling, reducing vasoconstriction and fibrosis	Evaluated in diabetic nephropathy and FSGS trials	Reduces proteinuria, stabilizes renal function; fluid retention remains a concern	[96–98]
Soluble guanylate cyclase (sGC) agonists	Enhance NO-sGC-cGMP pathway, improving renal perfusion and endothelial function	Phase II/III trials ongoing	Reduces albuminuria, improves renal blood flow; further validation needed	[99–101]
Angiotensin receptor-neprilysin inhibitors (ARNIs)	Combine neprilysin inhibition with AT1 blockade, reducing fibrosis and proteinuria	Evaluated in CKD and heart failure trials	BP control, modest albuminuria reduction, mixed eGFR effects	[102–104]

4.2.1. Direct renin inhibitors

In the realm of direct renin inhibitors (DRIs), aliskiren remains the most extensively studied and the only FDA-approved agent for clinical use in the treatment of hypertension, has demonstrated a notable efficacy in reducing proteinuria and slowing the progression of CKD by interrupting the RAAS cascade at its very inception[105]. Aliskiren act at the very first step of the cascade by blocking renin and thereby decreasing the formation of angiotensin I and, subsequently, angiotensin II[25]. Several clinical studies have evaluated the renoprotective effects of Aliskiren, particularly in non-diabetic CKD patients. According to a study by Li *et al*.[90], the effect of add-on Aliskiren therapy (150 mg daily) in 189 non-diabetic CKD patients receiving angiotensin II receptor blockers (ARBs) demonstrated a 26% reduction in urinary protein-to-creatinine ration and a smaller decline in glomerular filtration rate (GFR) as compared to ARB monotherapy, suggesting a potential benefit in proteinuria management. Another randomized controlled trial, Direct Renin Inhibition in Non-Diabetic CKD (DRINK) by Tang *et al*.[91], assessed the long-term safety and efficacy of Aliskiren in CKD stages 3–4 patients. While the study found no significant difference in the rate of eGFR decline between Aliskiren and ARB monotherapy groups, it reported higher incidence of hyperkalemia in the Aliskiren-treated cohort, highlighting the need for careful electrolyte monitoring[91]. Additionally, an open-label prospective trial demonstrated that Aliskiren add-on therapy significantly reduced proteinuria by 23% in CKD patients receiving ACE inhibitors or ARBs, reinforcing its potential role in dual RAAS blockade strategies[92]. Despite these promising findings, concerns regarding hyperkalemia and hypotension remain, necessitating further research to optimize its use in CKD management.

4.2.2. Aldosterone synthase inhibitors

Aldosterone synthase inhibitors (ASIs) such Osilodrostat, Baxdrostat, Lorundrostat, BI 690517, and DP-13 represent an emerging class of therapeutics targeting aldosterone synthesis by inhibiting CYP11B2, the enzyme responsible for converting 11-deoxycorticosterone into aldosterone[95]. These agents effectively reduce sodium retention, lower blood pressure, and attenuate renal fibrosis, addressing concerns about aldosterone escape despite RAAS inhibition[95]. However, challenges in off-target effects on CYP11B1-a key enzyme for cortisol synthesis — have complicated their clinical development[106]. Early ASIs, such as Osilodrostat, faced glucocorticoid suppression and compensatory increase in 11-deoxycortisterone (11-DOC), which limited their antihypertensive effects[107,108]. Recent clinical trials have further explored ASI efficacy: Baxdrostat showed significant blood pressure reduction in Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

(BrigHTN) trial[93], while the Efficacy and Safety of Baxdrostat in Patients with Uncontrolled Hypertension (HALO) trial reported no statistical benefit[93]; the ongoing trial: A Study to Evaluate CIN-107 for the Treatment of Patients with Uncontrolled Hypertension and Chronic Kidney Disease (FigHTN-CKD) will assess its renoprotective effect[109]. Similarly, Lorundrostat was assessed in the Trial on the Safety and Efficacy of MLS-101 in Patients with Uncontrolled Hypertension (TARGET-HTN) trial, where 50 mg daily reduced systolic BP by -9.6 mmHg, through concerns over modest potassium elevations (0.25–0.34 mmol/L) and hyperkalemia (>6.0 mmol/L in some participants) necessitate close monitoring [94]. Meanwhile, BI 690517, another investigational ASI, demonstrated a placebo-corrected 39.5% reduction in UACR in CKD patients receiving empagliflozin, supporting nephroprotective potential[110]. Additionally, DP-13, currently in phase II trials for primary aldosteronism, is being evaluated for aldosterone suppression and blood pressure control[111]. Despite hurdles, ASIs offer a promising approach for CKD and resistant hypertension, providing greater specificity and fewer off-target effects than earlier inhibitors.

4.2.3. Endothelin receptor antagonists

The endothelin (ET) system plays a crucial role in renal pathophysiology, contributing to vasoconstriction, inflammation, fibrosis, and proteinuria in CKD. Endothelin receptor antagonists (ERAs) such as Atrasentan and Sparsentan are promising nephroprotective agents targeting endothelin-1 (ET-1) signalling, a potent driver of renal vasoconstriction, fibrosis and hypertension[112]. Excess ET-1 levels contribute to glomerular injury, inflammation, and progressive CKD, making ERAs particularly beneficial in diabetic nephropathy and focal segmental glomerulosclerosis (FSGS)[113,114]. Atrasentan, a selective ETA receptor antagonist, was evaluated in the Study of diabetic Nephropathy with AtRasentan (SONAR) trial, which demonstrated a 35% reduction in proteinuria and stabilised renal function in diabetic CKD patients, reinforcing its potential renoprotective effects[97]. The study further highlighted Atrasentan's ability to lower albuminuria while minimising sodium retention, although fluid overload and heart failure risk remained key concerns[96]. Similarly, Sparsentan, a dual ETA and AT1 receptor antagonist, was assessed in the Prospective randomized study of the tolerability and efficacy of combination therapy (PROTECT) trial, where it achieved 50% reduction in proteinuria compared to 32% with irbesartan, with 42% of Sparsentan-treated patients achieving partial remission, significantly outperforming standard therapy[98]. Despite these benefits, fluid retention remains a major limitation, necessitating careful patient selection and monitoring. Given their strong antiproteinuric and antifibrotic effects, ERAs represent an important addition to CKD treatment strategies, particularly in cases where conventional RAAS blockade alone is

insufficient. Ongoing research continues to refine their long-term safety and efficacy, including potential combination therapies to mitigate adverse effects.

4.2.4. Soluble guanylate cyclase agonists

The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway plays a critical role in vascular homeostasis, renal perfusion and endothelial function. In CKD, oxidative stress impairs NO binding to sGC, reducing cGMP production, leading to vasoconstriction, endothelial dysfunction, and progressive renal fibrosis[115]. sGC agonists aim to restore cGMP levels by either directly stimulating sGC activity (sGC activators) or enhacing NO sensitivity (sGC stimulators), thereby improving renal blood flow, reducing oxidative stress and lowering albuminuria[100]. Notable sGC agonists include Vericiguat, a NO-dependent activator beneficial for advanced CKD. Runcaciguat, a highly selective sGC activator, has demonstrated significant nephroprotective effects in clinical trials, with randomised study showing 45.2% reduction in urinary albumin-to-creatinine ratio (UACR) compared to placebo[99]. The ongoing ALPINE-1 trial further evaluates BAY3283142 for its potential in improving endothelial function, renal blood flow, and proteinuria reduction[101]. Given their ability to complement RAAS inhibitors and SGLT2 inhibitors, sGC agonists hold great potential in CKD management. However, further research is needed to refine dosing strategies, assess long-term safety and explore combination therapies that maximize renal protection while mitigating adverse effects.

4.2.5. Angiotensin receptor-neprilysin inhibitors

Angiotensin receptor-neprilysin inhibitors (ARNIs) have emerged as a promising therapeutic strategy in CKD by combining neprilysin inhibition with angiotensin receptor blockade, offering dual protection against glomerular hypertension, proteinuria, and renal fibrosis[116]. The primary ARNI, Sacubitril/Valsartan, functions by inhibiting neprilysin, an enzyme responsible for degrading natriuretic peptides, thereby enhancing vasodilation, sodium excretion, and reducing cardiac and renal stress[102,117]. Simultaneously, Valsartan blocks angiotensin II receptors, preventing vasoconstriction, aldosterone secretion, and oxidative stress, which are critical drivers of CKD progression[102]. Through these complementary actions, ARNIs mitigate glomerular hyperfiltration and tubulointerstitial fibrosis, contributing to better long-term renal outcomes. Several clinical trials have assessed the efficacy of ARNIs in CKD. The United Kingdom Heart and Renal Protection-III (UK HARP-III) trial evaluated Sacubitril/Valsartan in patients with moderate CKD, demonstrating modest reduction in albuminuria but no significant improvement in eGFR

decline compared to ARB therapy alone[103]. Despite this, ARNIs showed benefits in blood pressure control and cardiovascular risk reduction, reinforcing their role in cardiorenal protection[102]. Trials in advanced CKD (stages 4–5) have also highlighted Sacubitril/Valsartan's ability to reduce proteinuria and attenuate renal fibrosis, particularly in patients with heart failure and preserved ejection fraction (HFpEF), where conventional RAAS blockade may be insufficient[104]. While ARNIs hold great potential for CKD management, especially in patients with concurrent heart failure and hypertension, concerns regarding excessive hypotension and long-term renal effects necessitate careful blood pressure monitoring, particularly in elderly or high-risk patients. As ongoing research continues to refine their optimal dosing and clinical indications, ARNIs may become a preferred therapeutic option for CKD patients, particularly those at high risk for cardiovascular complications and progressive renal decline.

4.3. Stem Cell Therapy and Regenerative Medicine

Stem cell therapy and regenerative medicine offer a novel approach to repairing damaged renal tissue by leveraging the regenerative potential of stem cells. Mesenchymal stromal cells (MSCs), derived from bone marrow[118], adipose tissue[119], or umbilical cord[89], have demonstrated anti-inflammatory, immunomodulatory, and antifibrotic properties, making them a promising candidates for CKD treatment[120]. Induced pluripotent stem cells (iPSCs), reprogrammed from somatic cells, can differentiate into kidney-specific cells, enabling the development of kidney organoids that mimic renal structures and functions[121]. Renal progenitor cells, found within the kidney, have the potential to repopulate injured nephrons and restore renal function. The therapeutic mechanisms of stem cells in CKD include direct differentiation into renal tubular cells and podocytes, paracrine signalling through growth factors and cytokines, and immune modulation to reduce chronic inflammation[122–124]. Clinical trials have shown that MSCs can reduce proteinuria and improve eGFR in diabetic nephropathy[125,126], while preclinical studies on iPSC-derived kidney organoids suggest their potential for renal tissue regeneration[121].

However, challenges such as optimal cell delivery methods, long-term engraftment, tumorigenicity risks and ethical concerns remain barriers to widespread clinical adoption. Future directions include combining stem cell therapy with biomaterials, gene editing technologies, and bioengineered scaffolds to enhance efficacy and durability.

4.4. Precision Medicine and Genomics in CKD

Advances in genomic technologies, including next-generation sequencing (NGS), whole-exome sequencing, and polygenic risk scoring, have enabled the identification of genetic variants associated with CKD progression and treatment response[127]. Monogenic kidney diseases, such as autosomal dominant polycystic kidney disease (ADPKD) and Alport Syndrome, can now be diagnosed through targeted gene panels[128], while complex polygenic forms of CKD are being unraveled through genome-wide association studies (GWAS) [74]. Integrative multi-omics approaches, combining genomic, transcriptomics, proteomics, and metabolomics, provide deeper insights into CKD pathophysiology[74]. Pharmacogenomics is emerging as a key tool in tailoring drug therapies, ensuring that patients receive treatments based on their genetic profile. For example, genetic variations in the CYP3A5 gene influence tacrolimus metabolism in kidney transplant recipients, guiding personalized immunosuppressive therapy[129]. Additionally, single-cell transcriptomics allows for the identification of disease-specific molecular pathways, enabling targeted interventions[130].

Despite these advancements, challenges such as data integration, high costs, and ethical concerns regarding genetic data privacy persist[74,127]. Future directions include standardizing genomic data protocols, developing AI-driven predictive models for CKD risk stratification, and expanding precision nephrology initiatives to improve patient outcomes.

4.5. Novel Biomarkers and AI for Prediction Models

Emerging biomarkers aim to provide greater sensitivity and specificity, enabling earlier diagnosis and personalized treatment strategies. Neutrophil gelatinase-associated lipocalin (NGAL) is a marker of acute tubular injury[131], while kidney injury molecule-1 (KIM-1) reflects proximal tubular damage[132]. Soluble urokinase plasminogen activator receptor (suPAR) has been linked to podocyte injury and inflammation, making it a potential predictor of CKD progression[133,134]. Cystatin C, an alternative to creatinine, offers a more reliable measure of renal function, particularly in elderly patients with low muscle mass or variable dietary protein intake[135].

The integration of multi-omics approach is revolutionizing CKD diagnostics by identifying disease-specific molecular signatures. Complementing this, artificial intelligence (AI) and machine learning are enhancing predictive modelling, enabling real-time risk assessment and treatment optimization. AI-driven models can analyze large datasets, integrating clinical parameters, imaging and biomarker profiles to predict rapid eGFR decline, renal replacement therapy (RRT) initiation and cardiovascular complications[136].

Similar to its application in natural product discovery from Streptomyces, where AI accelerates the identification of novel bioactive compounds and optimizes drug development pipelines, AI holds great promise in CKD for developing personalized care strategies. These systems can support real-time decision-making and therapeutic optimization by integrating biomarker panels, patient profiles, and disease dynamics[137].

However, challenges include biomarker standardization, large-scale validation and clinical integration. Future directions involve developing multi-biomarker panels, refining AI algorithms for CKD prediction and implementing AI-driven clinical decision support systems to improve patient outcomes.

4.6. Role of Microbiome and Gut-Kidney Axis

The gut-kidney axis represents the intricate relationship between gut microbiota and renal function, with growing evidence suggesting that gut dysbiosis contributes to CKD progression[138]. In CKD patients, alterations in gut microbiota composition leads to the overproduction of uremic toxins, such as indoxyl sulphate, p-cresyl sulphate, and triemethylamine-N-oxide (TMAO), which exacerbate renal inflammation and oxidative stress due to their accumulation in the bloodstream[139]. Additionally, intestinal barrier dysfunction allows bacterial endotoxins to translocate into circulation, triggering immune activation and systemic inflammation[140]. Therapeutic strategies targeting the gut microbiome include prebiotics, probiotics, dietary interventions, and faecal microbiota transplantation (FMT)[139–141]. High-fibre diets promote the growth of beneficial bacteria and encourages regular bowel movements, allowing uremic toxins to be excreted before entering systemic circulation[142]. Probiotic supplementation with commonly used strains such as *Lactobacillus* and *Bifidobacterium*, has shown potential in modulating gut microbiota and improving renal outcomes[141,143]. FMT, an emerging therapy, aims to restore microbial balance in patients with severe dysbiosis.

Despite promising findings, challenges such as variability in microbiome composition, lack of standardised interventions and limited clinical trials hinder widespread adoption. Future research should focus on identifying microbiome-based biomarkers for CKD progression, optimising microbiome-targeted therapies, and integrating gut microbiome data with precision medicine approached to enhance CKD management.

5. Challenges and Future Perspectives

Despite advancements in CKD management, several challenges persist, particularly in early diagnosis, equitable access to treatment, patient education, and targeted intervention

for high-risk populations. Early detection of CKD remains a significant challenge due to the lack of highly sensitive and specific biomarkers for identifying kidney dysfunction before irreversible damage occurs. This diagnostic gap often leads to late or ultra-late referral to nephrologists, where patients first present at advanced stages of CKD or even with end-stage kidney disease. Delayed referral limits the effectiveness of early interventions, reduces the opportunity for slowing disease progression, and increases the risk of complications, hospitalizations, and mortality. Traditional markers such as serum creatinine and eGFR often fail to detect early-stage CKD, leading to delayed intervention[131]. While emerging biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and urinary exosomal RNA show promise in detecting kidney injury earlier[144,145], their clinical validation and integration into routine practice across different healthcare systems contribute to delayed diagnosis, particularly in low-resource settings where access to nephrology care is restricted.

Artificial intelligence (AI) offers transformative potential in overcoming diagnostic limitations. AI-driven predictive models, trained on large datasets from electronic medical records (EMRs), can identify at-risk individuals earlier by detecting subtle clinical patterns and integrating multiple biomarkers. Machine learning algorithms can also enhance the accuracy of risk stratification, support clinical decision-making, and automate patient alerts for timely referrals. However, for widespread adoption, these tools must undergo rigorous clinical validation, regulatory approval, and cost-effectiveness analysis. Additionally, standardization across platforms and addressing algorithmic biases are essential to ensure equitable deployment in diverse patient populations[146].

Inequities in access to care still persist despite advancements in CKD management, which disproportionately affecting low-income populations and racial minorities[147]. Socioeconomic barriers such as lack of health insurance, geographic constraints, and limited availability of specialised nephrology services contribute to delayed diagnosis and suboptimal treatment[148]. Studies indicate that Black and Hispanic populations experience higher CKD prevalence and mortality rates, yet face greater obstacles in accessing early nephrology care, home dialysis options, and kidney transplantation[147]. Addressing these disparities requires policy-driven interventions, including expanding insurance coverage, increasing nephrology workforce distribution, and implementing community-based screening programs. Additionally, telemedicine and mobile health technologies could bridge gaps in care, particularly for rural and underserved populations, ensuring timely intervention and improved outcomes[147–149].

Another significant barrier to effective CKD management is low patient awareness and health literacy, leading to delayed diagnosis and poor adherence to treatment regimens. Many individuals remain unaware of their CKD status until advanced stages, exacerbating disease progression and increasing healthcare costs[150]. Educational initiatives aimed at improving public knowledge of CKD risk factors, symptoms and preventive measures are essential. Strategies such as interactive digital platforms, community outreach programs and multidisciplinary patient education sessions can empower individuals to take proactive steps in managing their kidney health[151,152]. Additionally, integrating CKD education into primary care workflows and using EMR-based prompts for screening and education can enhance early intervention[153]. Equipping healthcare providers with evidence-based communication tools is equally important to facilitate shared decision-making and improve adherence to treatment plans.

Targeting high-risk populations for early intervention is crucial in reducing CKD burden and preventing progression to end-stage renal disease (ESRD)[154]. Individuals with diabetes, hypertension, CVD and genetic predisposition require proactive screening and personalised treatment approaches. Tools like the KDIGO Early Identification and Intervention Toolkit emphasize the importance of stratified risk assessment, timely nephrology referrals, and personalized care plans[155]. In this context, AI can support precision medicine approaches by synthesizing patient-specific data to recommend individualized interventions based on risk profiles, lifestyle factors, and genetic predispositions[156]. To mitigate the global CKD burden, future efforts must focus on integrating early detection, personalized treatment, and patient-centered education into primary care models. Seamless collaboration between general practitioners, nephrologists, and digital health platforms will be essential to delivering timely and effective care. As molecular innovations continue to evolve, merging conventional strategies with AI-enhanced diagnostics and targeted therapies offers the potential to transform CKD management from a reactive to a proactive and precision-driven paradigm.

6. Conclusions

CKD remains a critical global health challenge, profoundly affecting patient quality of life, healthcare systems, and economies worldwide. Although traditional strategies have provided essential support in managing CKD, emerging advanced approaches offer transformative potential. However, successful translation of these innovations into routine clinical practice will require overcoming significant barriers, including issues of implementation, accessibility, and clinician awareness. Continued efforts in research, policy,

and clinical education are crucial to bridge the gap between emerging therapies and practical application. By overcoming current treatment limitations and embracing novel interventions, the future of CKD care may shift toward more effective, patient-centered management, ultimately improving prognosis and quality of life for affected individuals worldwide.

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