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Review Article

Hypertension in chronic kidney disease: pathophysiology and innovative treatment approaches

Habeeba Sulthana[1*], Shaik Harun Rasheed[2], Tirukondur Hima Bindu Kasyap[3], Lanjapally Laxmi[4], Raghavendra Kumar Gunda[5], Kosika Sandeep[6]

[1]Assistant Professor, Department of Pharmacology, Guru Nanak Institutions Technical Campus (school of Pharmacy), Ibrahimpatnam, Ranga, Reddy, Telangana, India -501506.
[2]Professor, Department of Pharmaceutics, Guru Nanak Institutions Technical Campus (school of Pharmacy), Ibrahimpatnam, Ranga Reddy, Telangana, India -501506.
[3]Assistant Professor, Department of Pharmaceutical Analysis, Guru Nanak Institutions Technical Campus (school of Pharmacy), Ibrahimpatnam, Ranga Reddy, Telangana, India-501506.
[4]Assistant Professor, Department of Pharmacology, Vignan Institutions of Pharmaceutical Sciences, Vignan Hills, Deshmukhi, Ranga Reddy, Telangana, India-508284.
[5]Associate Professor, Department of Pharmaceutics, Narasaraopeta Institute of Pharmaceutical Sciences (Autonomous), Narasaraopet, Palnadu (Dt), Andhra Pradesh – 522601.
[6]Assistant Professor, Department of Pharmaceutics, Guru Nanak Institutions Technical Campus (school of Pharmacy), Ibrahimpatnam, Ranga Reddy, Telangana, India-501506.

[*]**Correspondence**
Habeeba Sulthana
habeebapharma@gmail.com

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Hypertension is both a cause and a consequence of chronic kidney disease (CKD), creating a bidirectional relationship that exacerbates cardiovascular and renal complications. The pathophysiology of hypertension in CKD is multifaceted, involving deregulation of the renin-angiotensin-aldosterone system (RAAS), endothelial dysfunction, volume overload, and increased arterial stiffness. Additionally, uremic toxins and oxidative stress further amplify vascular injury and inflammation, contributing to the progression of both hypertension and renal impairment. Traditional antihypertensive therapies, including RAAS inhibitors, calcium channel blockers, and diuretics, remain central to management; however, therapeutic challenges persist due to CKD-associated pharmacokinetic alterations and patient heterogeneity. Recent advancements in treatment approaches have introduced novel pharmacological and non-pharmacological interventions. These include using sodium-glucose cotransporter-2 (SGLT2) inhibitors, which have demonstrated Renoprotective and blood-pressure-lowering effects, and non-steroidal mineralocorticoid receptor antagonists, offering improved safety profiles. Emerging technologies such as renal denervation and baroreceptor activation therapy provide innovative, non-invasive options for resistant hypertension. Additionally, personalized medicine approaches, including genomics and biomarker-based risk stratification, hold promise for tailoring interventions to individual patient profiles. This review highlights the intricate interplay between hypertension and CKD pathophysiology, discusses recent advancements in therapeutic strategies, and underscores the need for a multidisciplinary approach to optimize patient outcomes. By integrating cutting-edge research with clinical practice, future strategy can mitigate the dual burden of hypertension and CKD, reducing morbidity and mortality in affected populations.

Keywords: *hypertension, Chronic Kidney Disease (CKD), pathophysiology, innovative therapies, Renin-Angiotensin-Aldosterone System (RAAS)*

Introduction

Chronic kidney disease (CKD) is increasingly recognized as a systemic disease involving all organs, including the kidneys, but the degree of involvement in the cardiovascular system is most pronounced (Lydia 2023). Hypertension, together with CKD, is regarded as the central issue to be addressed because it increases the risk for end-stage kidney disease and is also a risk factor for cerebrovascular and systemic atherosclerotic and aorterioatherosclerotic events, as

well as a major contributor to the high prevalence of sudden cardiac death, arrhythmias, and heart failure. Chronic heart disease is the underlying cause of death in 40.6% of patients with a glomerular filtration rate <30 mL/min per 1.73 m². The presence of CKD accelerates the progression of chronic heart failure and is a strong and independent predictor of acute and chronic cardiovascular death in patients with chronic heart failure. Thus, the treatment of hypertension in CKD has become the most extensively researched and reported therapeutic measure. In this review, we discuss recent developments in the area and report on new treatment strategies, including a focus on adipocytokines, the use of SGLT2 inhibitors, gut microbiome, and FXR agonists, and microbiome-derived indole, to delay progression or blunt the onset of complications. SGLT2 inhibitors have a broad protective effect on the cardiovascular system from both a hemodynamic and a metabolic point of view. In the course of this article, we will delve deeper into recent discoveries in this area.

Prevalence and significance

Chronic kidney disease exacerbates hypertension and vice versa, leading to what is referred to as a multifactorial vicious cycle. Hypertension is a prominent feature of chronic kidney disease, particularly once microalbuminuria is found. The latter is a very frequent condition that also complicates the healthcare sector in developing countries. Nevertheless, awareness of kidney disease and its possibilities is substantially lower than the awareness of primary hypertension, and surveys reveal that patients recognize kidney disease at a smaller fraction than their primary disease. Therefore, in the evaluation, prevention, and management of hypertension, particular emphasis should also be given to cost-effective options for early recognition and therapy of accompanying kidney disease. As the Committee for Global Emergency and Cardiovascular Disease points out, despite advances in diagnostics and medication therapy, hypertension is poorly managed and a leading risk factor for morbidity and mortality worldwide. In addition, it is a poorly managed or regulated risk factor (Targher et al., 2023). The latter declaration is supported by the observation that only one in four persons in high-income countries complies with the blood pressure control goals provided in recent guidelines. It does not result in better outcomes across therapeutic thresholds and has implications in terms of cost compared with alternative approaches that focus on cardiovascular and renal protection. This should make us reconsider our attitudes toward identifying and managing kidney disease in the context of the hypertensive patient. Patient Characteristics and Risk Factors for Hypertension in CKD Summarized in **Table 1**. In this chapter, after introducing the information that backs up suggestions outlined in guidelines for chronic hypertensive patients, we will attempt to do exactly that. Since we explore the problem of hypertension and severe kidney disease, we will not be able to provide a thorough, systematic overview of approaches to handling other kidney disorders. Since anti-hypertensive treatment aimed at blocking the "triple hit" of afferent and efferent glomerular arterioles and interstitial resistance seemed promising outcomes in other primary kidney disorders, we will leverage specific knowledge about the pathophysiology of chronic kidney disease.

Table 1. Patient characteristics and risk factors for hypertension in CKD

Category	Characteristics	Examples	Reference
Demographic Factors	Age, gender, and ethnicity	Advanced age, male gender, African ancestry	(Hong et al., 2023)
Lifestyle Factors	Diet, physical activity, and substance use	High salt intake, sedentary lifestyle, smoking	(Ozemek et al., 2020)
Genetic Factors	Family history of hypertension or related disorders	Parental hypertension, genetic mutations in RAAS	(Barua et al., 2022)
Comorbidities	Pre-existing medical conditions contributing to elevated blood pressure	Diabetes, obesity, dyslipidemia	(Chakraborty et al., 2023)
Environmental Factors	Living and working conditions that influence stress or health	Urbanization, noise pollution, occupational stress	(Habas et al., 2023)
Psychosocial Factors	Psychological stress, mental health conditions, and socioeconomic status	Anxiety, depression, low income	(Bhavsar et al., 2021)

Pathophysiology of hypertension in chronic kidney disease

Association of Hypertension and Chronic Kidney Disease Hypertension is a well-established factor in the progression of kidney damage, making the relationship between CKD and HTN often depicted as a vicious cycle. The analysis concluded that patients with CKD were significantly more likely to require the treatment of essential HTN compared to those without CKD. Several theories have been proposed to explain mechanisms linking HTN to CKD and vice versa. They include the role of HTN in the induction of an increase in the internal renal pressure and activation of the renin-angiotensin system, favoring pathological processes in glomerular and tubulointerstitial compartments, such as

glomerulosclerosis, vasomotor dysregulation, and injury to the renal endothelium; impaired pressure-natriuresis; damage to systemic endothelial function; increased vascular stiffness; activation of pro-inflammatory, pro-oxidative, pro-fibrotic, and proliferative signaling processes; and others [refer to Figure 1]. Moreover, it is now well recognized that hypertension can lead to renal hypoxia due to inadequate dilation of afferent arterioles in the case of increased renal tissue oxygen demand to mitigate impairments of oxygen delivery, as well as changes in mitochondrial function (Magley et al., 2024). Moreover, hypoxia may activate hypoxia-inducible factor-1 alpha, which might lead to the expression of various pro-fibrotic genes, apoptosis, and profibrotic signaling.

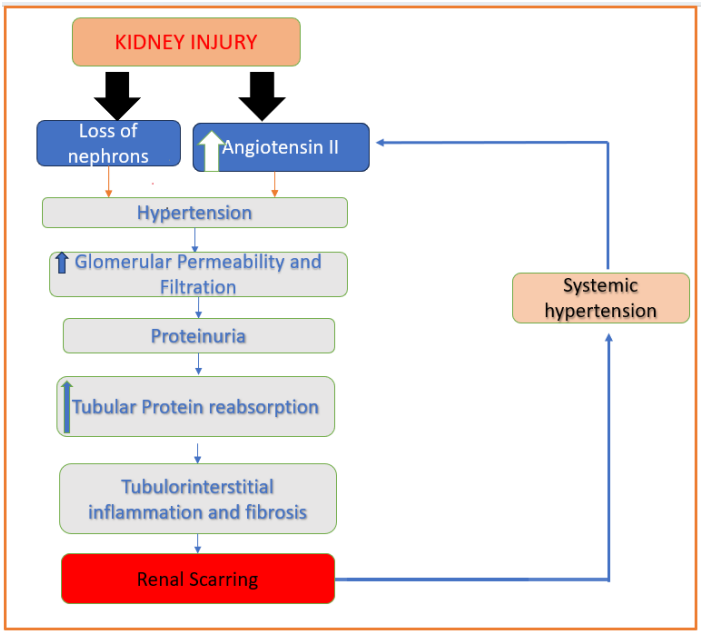

Figure 1. Pathophysiology of Hypertension in Chronic Kidney Disease

Renin-Angiotensin-Aldosterone system

The Renin-Angiotensin-Aldosterone System (RAAS) is one of the main regulatory mechanisms for the volume and electrolyte balance of the organism (Fountain et al., 2024). To a large extent, it plays a role in the adaptation of the organism to the loss of circulating blood volume. The kidneys can detect such a decrease and change the production of renin. In response to low blood volume, the secretion of renin is increased, which in turn cleaves the 10-amino-acid-long angiotensin I peptide from a large glycoprotein also known as angiotensinogen. Angiotensin I is then converted into an 8-amino-acid-long angiotensin II by angiotensin-converting enzyme, which is mainly found in the pulmonary endothelium entering and leaving the lungs. The amount of renin in the circulation determines the activation of RAAS. The level of renin is regulated by numerous mechanisms, including macula densa reflex, activation and inactivation of the renal sympathetic nerves, altered blood flow within the arterioles of the kidneys, and many other regulatory pathways. The concentration of angiotensin II in the blood is typically low but is significantly increased during blood loss. It is responsible for stimulating the thirst center in the hypothalamus and increases the secretion of vasopressin. On the other hand, as a strong vasoconstrictor, it causes an increase in pressure in the arterial system and, in combination with aldosterone.

Clinical manifestations and complications

Cardiovascular disease is the leading cause of mortality in kidney failure patients. Cardiac morbidity and mortality typically exceed a patient's risk of progressing to end-stage renal disease. The reduction of kidney function corresponds to the development of structural changes in the heart and blood vasculature, along with contractile dysfunction of the left ventricle. The diminished bioavailability of nitric oxide, oxidative stress, the activation of the local and systemic renin-angiotensin system, and abnormalities in calcium and cation channel activities are predominant contributors to vasoconstriction and structural changes in the blood vasculature. Activation of the sympathetic nervous system supports cardiac alterations, including increases in afterload and preload in chronic kidney disease. Blood pressure increases in approximately 80-85% of patients with advanced chronic kidney disease and in almost 100% when glomerular filtration rates fall below a certain level. There is convincing evidence that a reduction of glomerular suction pressure supports slowing the progression of kidney injury to end-stage renal disease in a significant percentage of patients previously

defined as "hypertensive nephrosclerosis" (Costantino et al., 2021). Counterregulatory mechanisms such as glomerular-efferent vasoconstriction and activation of the local and systemic renin-angiotensin system support glomerular filtration; however, kidney function deteriorates with time. High systolic blood pressure is a negative prognostic parameter in patients affected by chronic kidney disease, even when kidney function is only slightly diminished. Blood pressure goals for patients with chronic kidney disease should be < 130/80 mm Hg, and a value ≤ 120/80 mm Hg should be the therapeutic goal for those patients in whom the rates of excretion of micro- and macromolecular organic molecules significantly differ from controls. Dietary salt restriction and lifestyle modifications should be implemented in managing these patients, as most are overweight and have hypertension due to an inadequate lifestyle.

Cardiovascular events

End-stage kidney disease (ESKD) patients on hemodialysis have a very high risk of cardiovascular morbidity and mortality (Kim et al., 2021). In fact, dialysis patients' hospitalization and mortality rates due to cardiovascular causes remain 10 to 30 times higher than in the general population. Evidence derived from epidemiological studies has demonstrated a high prevalence of traditional and non-traditional cardiovascular risk factors in ESKD patients. Traditional cardiovascular risk factors include older age, sex (male), smoking, diabetes, hypertension, obesity, dyslipidemia, a sedentary lifestyle, and a positive family history of coronary artery disease. Increased arterial stiffness, high peripheral vascular resistance, atherosclerosis, reduced coronary and peripheral blood flow, volume overload, autonomic dysfunction, anemia, microinflammation, dyslipidemia, homocysteine, and disturbances in calcium-phosphate metabolism, left ventricular hypertrophy (LVH), and functional and structural myocardial ischemia are some examples of the non-traditional cardiovascular risk factors identified in uremic patients.

Diagnostic approaches

The diagnosis of hypertension in patients with chronic kidney disease is straightforward but can be challenging due to the "white coat" effect (Singh et al., 2023). Noninvasive measurements of blood pressure may be less accurate than intra-arterial blood pressure measurements, but 24-hour monitoring is frequently used to document hypertension before starting treatment. Central blood pressure and aortic stiffness are good indicators of cardiovascular risk in chronic kidney disease patients, and an increase in central blood pressure may warrant an increase in the blood pressure target. The prevention and management of chronic kidney disease patients with diabetes and hypertensive disorders must follow the clinical practice guidelines. The choice of antihypertensive drugs should be individualized. The basis of the therapy is the blockade of the renin-angiotensin system due to its beneficial hemodynamic and non-hemodynamic actions. It appears that the direct renin inhibitors and angiotensin II receptor blockers have similar renoprotective properties in patients with chronic kidney disease who previously developed angiotensin-converting enzyme inhibitor cough, but regular monitoring of hyperkalemia and renal function is necessary. The combination of a direct renin inhibitor with an angiotensin II receptor blocker could further activate the renin-angiotensin system by activating the (pro)renin receptor. The role of sodium-glucose cotransporter-2 inhibitors and mineralocorticoid antagonists in the management of chronic kidney disease-associated hypertension and for the slowing down of kidney function remains to be elucidated. Conversion of blood pressure measurements to central blood pressure and 24-hour ambulatory blood pressure monitoring is encouraged in hypertensive patients with chronic kidney disease.

Blood pressure measurement

Blood pressure should be routinely measured in patients with chronic kidney disease (CKD), as it provides essential diagnostic and prognostic information. Blood pressure is subject to substantial inter- and intra-individual variability, including "white coat" and "masked" hypertension effects, plus "terminal digit preference"—all of which can also introduce errors in both routine clinical practice and clinical trials. There are four different techniques for measuring blood pressure: casual or clinic blood pressure, self-measured blood pressure at home, 24-hour ambulatory blood pressure, and blood pressure evaluated in a renal clinic or research unit—either initially or as a supplement to guide management (Bress et al., 2024; Ray et al., 2023; Goyal et al.,2023; Kashani et al., 2022). The results of these four different techniques should yield similar information. However, the relationships can be discordant. Therefore, what is the best method for assessing blood pressure in clinical practice to find out, this text will review the physiological basis for variations in blood pressure, the meaning of the data obtained by the four different methods, the management of blood pressure in the renal patient, and the likely future directions.

Conventional treatment strategies

Patients with CKD need to be treated with a combination of antihypertensive medications to ensure comprehensive control of blood pressure (Ohno et al., 2022). It is crucial to consider the effect beyond blood pressure control as well as

factors such as albuminuria control via the use of renin-angiotensin-aldosterone system blockers. In those with diabetes, glycemic control is also important. Thiazide diuretics and thiazide-like diuretics seem to preserve GFR and reduce albuminuria to a greater extent than other antihypertensive medication classes. A meta-analysis of trials comparing blood pressure-lowering drugs showed that dihydropyridine calcium-channel blockers were more effective in the control of albuminuria than blockers of the renin-angiotensin-aldosterone system or angiotensin-converting enzyme when blood pressure-lowering efficacy was matched. This may influence the progression of CKD favorably. In patients with stage 3 or 4 CKD, blood pressure-lowering therapy only with blockers of the renin-angiotensin-aldosterone system and non-dihydropyridine calcium-channel blockers is renoprotective when compared to hydrochlorothiazide and amlodipine. Importantly, for the progression of end-stage renal disease, perindopril was shown to be superior to losartan, suggesting that the high risk at which these patients are placed is in favor of drugs with a broader target within the renin-angiotensin-aldosterone system. Given the evidence supporting the more widespread use of thiazide and related diuretics in these patients, there is no evidence from randomized controlled studies that the combination of inhibitors of the renin-angiotensin-aldosterone system with thiazide diuretics is renoprotective, and its peptide profiles and metabolite excretion remain unknown.

Antihypertensive medications

For kidney protection, there are some preferred antihypertensive medications administered for chronic kidney disease (CKD). Inhibitors of the renin-angiotensin-aldosterone system (RAAS) such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers interrupt the negative effects of RAAS on the kidney. Guidelines recommend their prescription in cases of impaired renal function, especially with a serum creatinine level <1.5, albuminuria, or proteinuria. Studies have shown that administering ACE inhibitors and ARBs together in patients with severe chronic kidney disease did not elicit a kidney function benefit and led to hyperkalemia, raising concerns about toxic effects. If patients are unable to take the medication due to side effects, however, ACE inhibitor doses should be reduced to manage them, following the physician's suggestion. In the absence of side effects, the ACE inhibitor doses should ideally be adjusted gradually and separately if necessary. Before discharging the patient, many researchers have suggested that patients with CKD should be given full doses of ACE inhibitors and ARBs, as well as proper monitoring.
Another RAAS-hypoactivity strategy involves the improvement of kinin-nitric oxide metabolism and reactive oxygen species generation by inhibiting enzymes. ACE inhibitors inhibit the classic conversion of angiotensin I into angiotensin II, resulting in bradykinin accumulation and nitric oxide activity, as well as blocking the non-canonical conversion of angiotensin I into angiotensin II (Cutrell et al., 2023). Studies have also shown that both ACE inhibitors and angiotensin receptor blockers have additional beneficial effects in decreasing inflammation, fibrosis, and thrombosis in the kidney independent of their blood pressure-lowering effects. ACE inhibitors are also somewhat effective but less so in lessening mortality compared to other antihypertensive medications. Data on the clinical consequences of conducting RAS-maintenance treatment plus RAAS inhibitors in blood pressure treatment have helped to better explain the harm of ACE inhibitors and ARBs.

Innovative treatment approaches

In the last few years, multiple chains of evidence based on pharmacological and epidemiological bases have indicated an essential role of eicosanoids as possible future druggable pathways. Clinical and experimental studies indicate that dual cyclooxygenase and lipoxygenase inhibitors could have a potential therapeutic role in slowing down the progression of chronic kidney disease and hypertension. The primary determinant of the production of vasodilator eicosanoids in systemic circulation is the production and activity of soluble epoxide hydrolase. Experimental studies in various murine models of spontaneously hypertensive rats showed that soluble epoxide hydrolase activity is significantly decreased, resulting in a substantial increase in the level of vasodilator eicosanoids, leading to a decrease in sympathetic nervous system activity and renal inflammation and fibrosis (Kozioł-Kozakowska et al., 2024). These studies provided indirect evidence for the possible beneficial role of soluble epoxide hydrolase in ameliorating forward heart failure-induced renal disease. In recent years, epoxy eicosanoid analog drugs, which are more effective in resistant hypertension, chronic kidney disease, cardiorenal syndrome, and metabolic syndrome, are in the preclinical and clinical stages of development. Since the efficacy of combined renin-angiotensin inhibition, a common therapy for hypertension that can damage the kidneys may be partially due to its positive effects on the interplay of soluble epoxide hydrolase and eicosanoids, inhibitors, when used early in the treatment, would exhibit significant cardiorenal-protective activity. These promising new data now suggest that targeting the production and activity of epoxyeicosatrienoic acid, as well as the endothelin B receptor, is worth the investment to mitigate the sympathetic reduction in chronic kidney disease. These future cardiovascular-renal therapies offer the hope that aggressive use of combination antihypertensive strategies will do a better job of serving as a transformational catalyst to uncover new cardiovascular-renal drugs than the limited array of antihypertensive targets currently does. Additionally, for this purpose, the unique pathophysiology of the

interaction of the cardiac and kidney tissues represents therapeutic levers that have been little studied and thus underappreciated, suggesting novel treatment targets for further in-depth investigation.

Renal denervation therapy

Renal Denervation Therapy: Renal denervation therapy is one of the most widely used techniques to reduce the activity of the renal sympathetic nerves that play a key role in controlling blood pressure (Mahfoud et al., 2022). RDN reduces BP in some patients, particularly in its early phase of treatment. There are three kinds of RDN technologies: radiofrequency-based, ultrasound-based, and endovascular catheter-based. These technologies are currently being used in clinical diagnosis. With the development of related technology, the range of application of renal denervation therapy has been expanded. It is the rehabilitation of patients with chronic kidney disease stage V, maintenance hemodialysis patients, and patients with glomerulonephritis who are treated with endovascular catheter-based ultrasound RDN. RDN therapy should be deemed a safe add-on treatment in hypertensive CKD patients with volume overload. There is considerable evidence that renal artery denervation can have significant antihypertensive effects in patients. However, the impact on kidney function could be relevant in a population at high risk for chronic kidney disease, and whether renal denervation may have other beneficial effects in CKD will not be clarified until future, better-powered studies are performed. It will require future collaborative trials in those without high BP to ascertain the clinical utility of this treatment. The improvement of the outcome of CKD can be held back to some extent.

Nutritional and lifestyle interventions

Nutritional and lifestyle interventions have a major role in the management of early to moderate chronic kidney disease (CKD). It has been demonstrated that Western diet trends are a cause for concern (Alkhatib et al., 2023). To improve treatment efficacy and quality of life without the use of a large number of drugs and to catalyze reno-protection through more proactive and accessible attitudes for nephrologists, the use of nutritional diets is crucial. In recent years, there have been interesting and numerous works that suggest the importance of personalized nephro-dietology in terms of protein intake and the quality of the diet, the use of various vitamins and minerals, carbohydrates, oral iron, and trace elements. Dietary proteins are emphasized as nitrogen metabolism may worsen in CKD because of fewer available nephrons. Excess dietary protein promotes glomerular hyperfiltration and accelerates the progression of CKD. A high-protein diet increases the kidney's workload. The excretory stress on the kidneys increases, and there is a greater load of nitrogenous metabolites; foraminal reflux and functional nephrons are damaged. The guidelines on nutrition in CKD suggested a low-protein diet for patients with or at risk of CKD. Proper protein and phosphorus intake limits should be observed in animal proteins. Although animal diets are rich in phospho-proteins, there are many human foods of plant origin that are low in phosphorus. Many foods rich in phosphorus, such as tomatoes, are normally consumed by dialysis patients since they contain less bioavailable phosphorus.

Dietary sodium restriction

Over the last few decades, dietary sodium has been significantly linked with the risk of cardiovascular disease, including hypertension. Consequently, dietary sodium restriction has been recommended as the cornerstone of non-pharmacological therapy in patients with various degrees of kidney dysfunction and urinary albumin excretion rate, as well as in chronic kidney disease, hypertension, and left ventricular hypertrophy (Sinclair et al., 2023). Current dietary sodium consumption by humans seems far beyond the requirements for sustained effective homeostasis. The dramatic increase in the use of processed foods worldwide within the last few years is more than sufficient to maintain sodium homeostasis, as documented by the increasing prevalence of salt sensitivity and the disproportional relationship between urinary sodium excretion and plasma aldosterone activation. Therefore, individuals or animal species may respond differently to dietary sodium load, as seen in the upper tertile of the population receiving urinary sodium excretion. However, a more likely explanation might be a more heavily salt-loaded diet that is less effective in providing a reno-protective response against increasing sodium intake. Indeed, dietary sodium regulation throughout a broad spectrum of individuals and animal species in response to dietary composition may be severely impaired. Subsequently, guidelines have emphasized the importance of dietary sodium intake in regulating blood pressure. In support of the physiological pattern of sodium handling by the kidneys in response to dietary sodium intake, a greater sodium intake is associated with an increased prevalence of insulin resistance.

Pharmacological advances

The pharmacological strategies mostly involve targeting an independent risk factor, cardiovascular disease, in chronic kidney disease, argued quite differently from other hypertensive diseases in such a way that nontraditional strategies will be preferred over traditional ones. Thiazide diuretics historically have been and still are a cornerstone in the

treatment of essential hypertension due to their robust antihypertensive efficacy and favorable cardiovascular outcomes (Lin et al., 2023). Despite all the beneficial effects, the data on diuretics exerting a modest cardiovascular outcome benefit in hypertension coexisting with various degrees of kidney function impairment are unexpectedly limited. Loop diuretics are the mainstays of symptomatic relief in heart failure, advanced cirrhosis, and acute kidney injury, just to mention a few clinical conditions that rapidly respond to natriuresis. Limiting free water, side effects, easy induction of volume depletion, refractoriness to the diuretic effect, and reduced efficacy in patients with chronic kidney disease are a few clues of where diuretic-resistant fluid overload has been anchored in the physiology of chronic kidney disease, including hypertension. Consequently, loop diuretics must be effective by requiring high doses for being inefficient in subjects with advanced kidney disease. Accordingly, they all found that in proportion to GFR, fewer patients had a brisk response to furosemide than they had to hydrochlorothiazide. In these studies, the subjects who were unresponsive to large doses of furosemide and needed the addition of hydrochlorothiazide also had fewer nephrons and were the patients who were at higher risk of developing nephropathy with hypertension.

Novel drug therapies

Chronic kidney disease (CKD) inevitably leads to end-stage renal disease, cardiovascular events, and shortened life expectancy due to the inevitable consequence of unrelenting hyperfiltration that occurs during progress along the course of this disease. Thus, novel therapy targeted at the early stages of pathophysiological mechanisms that underlie hyperfiltration could delay the onset and progression of CKD, concomitant with a reduction in blood pressure and albuminuria. Furthermore, selective improvement of natriuresis in the thick ascending limb should lead to suppression of the epithelial Na+ channel, and because activation of this channel is critical for the development of the Th2 phenotype of tissue-resident Th-ch2 cells, suppression could attenuate inflammation and fibrosis. Renin-angiotensin-aldosterone blockers and compounds that block the direct mechanism, the glomerulotubular balance, or the tubuloglomerular feedback mechanism result in exacerbation of compensatory hyperfiltration (Jeffery et al., 2022). Blockade results in suppression of renal hyperfiltration after subtotal nephrectomy and the induced increase in the glomerular pressure-to-producing hydrostatic pressure ratio. Calculated fractional distal Na+ delivery in the thick ascending limb and distal nephron, as well as expression of NCC and the epithelial Na+ channel, were suppressed, suggesting that the derived nitric oxide in the thick ascending limb plays an important role in mediating pressure natriuresis in intact animals. Inhibition for 10 days increased glomerular mesangial area and expression of mesangial collagen type IV and fibronectin proteins, as well as renal expression of various profibrotic genes, indicating that the derived nitric oxide in the thick ascending limb also mediates the antifibrotic effect in CKD.

Complementary and alternative medicine

Traditional modalities have been and continue to be used by a wide percentage of the patient population. These agents are widely utilized by ethnic groups, especially those from Asia who place greater importance on and utilize the knowledge obtained from, their ancestors. It is presumed that the knowledge and wisdom of this age tend to transcend future generations and are possibly successful in treating a host of renal or systemic illnesses. However, deciphering the mode of action and conducting large-scale, well-conducted clinical trials to examine their efficacy and safety have been lacking. Several Ayurvedic, Unani, Homeopathic, Persian, and Traditional Chinese medicines have been used for centuries to treat various forms of kidney disease (Walia et al., 2023). Unfortunately, until recently, very few have undergone scientific scrutiny or large-scale clinical trials. A large body of evidence exists to demonstrate that all disciplines of Complementary and Alternative Medicine can enjoy contemporary evidence-based investigation. The wide and expanding utilization of these therapeutic options can no longer be ignored by orthodox medical care. It is hoped that new scientific insights from herbs and other complementary medicine disciplines will provoke physicians to think about failures in the conventional approach, leading to improved attitudes in the care of patients with, or at risk for, chronic kidney disease. In this chapter, we will briefly review potential beneficial applications of the different approaches used in Unani, Homeopathic, Persian, and Traditional Chinese medicine for the treatment of primary and hypertension-related renal diseases (Metwally et al., 2023).

Acupuncture

Acupuncture is an ancient treatment and is considered safe. It acts through the regulation of a variety of chronic diseases by stimulating the nerve endings in the skin, muscles, and other tissues. The treatment of patients with acupuncture in the cardiovascular system is beneficial and safer than drug therapy (Wang et al., 2023). It is beneficial for the gradual decrease in blood pressure and the stability of blood pressure in both hypertensive patients and those with chronic kidney disease. So far, there have been a few studies on the therapeutic effects of acupuncture on the pathophysiological process of hypertension induced by chronic kidney disease. The precise molecular mechanisms that regulate this effect are still not well defined. However, the results of these studies suggest that it could be an alternative intervention

method in the clinical management of hypertension in chronic kidney disease and, similarly to other conditions, can be used as a supplement to conventional treatments. Using animal experiments, it has been observed that the sympathetic nervous system can be significantly regulated, regardless of the level of serum CRE or ET. This can be alleviated by reducing the level of low-grade inflammation, oxidative stress, and inflammatory cytokines (Fan et al., 2023). Its characteristics of having few side effects and being simple to operate, particularly for those patients resistant to conventional antihypertensive drugs, could therefore be a great substitute for future treatment strategies for hypertension in patients with chronic kidney disease. However, the details of the activating acupuncture point, frequency, strength, and other specific efficacy have not been definitively explored, and therefore basic research for this intervention is required.

Patient education and self-management

Treatment of hypertension in chronic kidney disease, especially in non-dialysis settings, requires patient education, including self-monitoring and self-management. The treatment goal is to tailor blood pressure control to the individual patient, accounting for the overall cardiovascular risk, the patient's life expectancy, as well as the presence of or risk for chronic conditions that are associated with detrimental sequelae of overly aggressive blood pressure management (Patil et al.,2023). There are no large randomized controlled trials in chronic kidney disease patients on optimal blood pressure targets, the best classes of antihypertensive drugs, or ideal pharmacological regimens to use; we therefore have to extrapolate and test trial evidence from large and multiple comorbidity patient populations. Moreover, the effective use of available antihypertensive drugs, as well as the renal protective potential of novel renal-specific or selective drugs, are major clinical goals that drive their exploration. Self-management of blood pressure involves empowerment of the individual patient through education to participate actively in the treatment, proper use of equipment, and in the best case might increase the drug-free period by substitution of medication to prevent over-treatment. Similar to other chronic diseases where the patient has to be involved in decisions of care, self-management can be as effective as usual care, at least when empowering education for self-management is implemented. However, few studies evaluated the strategy of using a therapeutic approach focusing on the patient gaining independence and guidance, counseling, exercise, and pharmacologically increased drug compliance. The drawback might be that patients' reports can be influenced by measurement methods and the time of day when measurements are performed. Further, significant inter- and intraindividual variabilities have to be anticipated. Blood pressure can be influenced by commonly ingested food, exercise, psychosocial stress, and alcohol or caffeine-related influences (Manalili et al., 2022). Moreover, metabolic syndrome, volume overloading due to poor dietary and fluid intake, and relative anemia can be associated with variable blood pressure measurements. Especially in the setting of chronic kidney disease with prevalent polypharmacy, accurate communication is needed to prevent medication errors, especially when utilizing correspondingly numerous antihypertensive agents with overlapping effects or interacting drugs. Special attention has to be paid to potential drug-induced adverse effects, especially dizziness and orthostatic hypotension which are linked to an increased incidence of falls.

Importance of medication adherence

Poor medication adherence was associated with 23% increased odds of requiring renal replacement therapy compared with adherent patients. Conversely, each 50% increase in the proportion of days covered was associated with an 18% decreased risk. Adherence to antihypertensives decreased from 60% during stage 1 CKD to 40% in stage 5, although it increased to 87% after starting dialysis. Control of blood pressure also improved; after starting dialysis, the probability of achieving a target blood pressure below 140/90 was 4% higher compared with before starting renal replacement therapy (Martell Claros et al., 2022). It is important to mitigate the adverse cardiovascular effects from poor blood pressure control, inflammation, and oxidative stress associated with antihypertensive use by utilizing general pharmaceutical care principles, such as educating the patient about the importance of adherence, teaching dosing schedules compatible with daily dialysis sessions, and counseling regarding potential side effects necessitating discontinuation. Encouraging family support surrounding medication use can also be beneficial when caring for patients on in-center dialysis.

However, despite a wide array of blood pressure medicines and vigorous treatment guidelines, blood pressure control is particularly difficult to achieve in patients with CKD. Some common properties of common diuretics are summarized in Table 2.

Table 2. Properties of Common Diuretics

Class	Mechanism of Action	Common Side Effects	Reference
Thiazide Diuretics	Inhibit Na^+/Cl^- symporter, reducing sodium and water	Hypokalemia, hyponatremia, hyperglycemia	(Georgianos PI et al., 2023)

	reabsorption		
Loop Diuretics	Inhibit $Na^+/K^+/2Cl^-$ symporter, causing significant natriuresis	Hypokalemia, hypomagnesemia, ototoxicity	(Lava SAG et al., 2023)
Potassium-Sparing Diuretics	Block aldosterone (spironolactone) or Na^+ channels (amiloride)	Hyperkalemia, gynecomastia (spironolactone)	(Lin Z et al., 2021)
Carbonic Anhydrase Inhibitors	Inhibit carbonic anhydrase, reducing bicarbonate reabsorption	Metabolic acidosis, paresthesia	(Aslam S et al., 2023)

Multidisciplinary care approach

Patients with CKD require multidisciplinary care services to enhance adherence to therapy and diet and to address cardiovascular risk factors. These patients need to be seen by a multidisciplinary team including a clinical pharmacist, psychologist, and dietitian. These specialists focus on the necessity of compliance with the care guidelines and the importance of medication and diet, and provide training to enhance food-item education, as well as fluid and salt-restriction education during the visit to ensure effectiveness (Borrayo-Sánchez et al., 2023). The use of daily diaries for medication and liquid tasks, along with the effect of diet education from a dietitian, and different educational methods and nutrition situations can be employed to improve the effectiveness of dietary guidelines for practical experience and reinforcement. At our clinic, patients who cannot fully understand or who often forget to follow the restrictions are also examined by psychologists. Considering it is evident that the patient's emotional feelings and perceptions play a significant role, and that a social support network for a patient’s adherence to changes in life should be created and strengthened, we try to improve their compliance rate together with family psychology workers. The multidisciplinary clinic setup combined with a 6-9 month exercise program from Nephrology, Cardiology, Nutrition, Ophthalmology, Physiatry, and Endocrinology gains greater physiological benefits as a clinical effect or social relationship support on medication compliance and dietary adherence in adults with non-dialysis CKD. At the same time, comorbidities such as diabetic retinopathy, sarcopenia, and cardiac diseases can be managed in patients with CKD. The treatment plan can be mindful of subjective medical care as well as cooperation within different disciplines, and there will be multiple multidisciplinary clinic evaluations designed to ensure coordination of care, reinforcing and intensifying relationships built on the establishment of the patient, and closing the gap between usual operations and successful health management. The aim is to make hourly recommendations and ways of incorporating health changes in such a way that it will positively impact future clinical outcomes and the everyday life, well-being, and safety of patients with CKD.

Role of nephrologists and cardiologists

Hypertension is highly prevalent in the population with chronic kidney disease (CKD) and end-stage kidney disease (ESKD), and aggressive blood pressure (BP) reduction is associated with decreased cardiovascular events and likely renal injury progression. Many patients can achieve target BP goals, including those on dialysis (Kouidi E et al., 2024). Current guidelines provide less guidance on specific antihypertensive agents, treatment regimens, or adjunct plans to control BP in the CKD population. The renal medulla and the sympathetic nervous system (SNS) have well-described roles in renal and overall cardiovascular hemodynamic control, largely through their effect on sodium and water balance. Because of this, antihypertensive therapies that affect these biological effectors might provide additional BP, volume, and kidney functional changes. SNS blockade is now moving to the forefront as a guide for BP control in the CKD population, and SNS-directing antihypertensive medications provide both BP control and frequently result in additional beneficial renal and cardiovascular influences. The kidney and heart interact and appear to communicate bidirectionally, and in this review, we summarize the intriguing hypothesis and rationale for collaboration between nephrology and cardiology in the BP care of the CKD population. It is widely appreciated that CKD is associated with both increased cardiovascular events and all-cause mortality. Given this significant link, it is desirable to consider holistic BP control strategies for improved global outcomes in CKD and ESKD. The kidney is the chief regulator of blood pressure (BP) and therefore plays a central role in cardiovascular risk. Importantly, the association between various other organs, including the heart, and control of BP has been known for some time, and involvement with these organs may provide new treatment strategies (Chopra et al., 2023). We begin our review with this fundamental area of cardiovascular and renal interaction, followed by a rationale for the study of the links between the heart and kidney, with specific reference to understanding these interactions in patients with both CKD and hypertension. We conclude by discussing past and future trials and considering the potential place of nephrologists and cardiologists in both the future and the present.

Future directions in research

Although RDN did not prevent the occurrence of overt clinical albuminuria in CKD patients with mostly normal blood pressure and albuminuria upon study entry, it considerably delayed the time to onset of clinical albuminuria and, when albuminuria occurred, it was significantly attenuated. For kidney function assessed by creatinine clearance, no benefit was demonstrated. Thus, RDN did not have a significant impact on GFR decline (Lenders et al., 2020). Compelling experimental research that investigates the potential mechanisms of such renal protective effects of RDN in the absence of blood pressure changes is currently lacking but is warranted. Such research should include an assessment of the effects of RDN on renal tissue oxygenation, erythropoietin production, and the renal response to different stimuli, e.g., ischemia, hypoxia, or hypovolemia. As discussed above, cellular oxygen sensing in the diseased kidney is deregulated, leading to pathological increases in oxygen consumption and uptake. Inappropriate local hypoxia is a key characteristic of this Patho mechanism. Our finding that lowering the oxygen demand of the kidney can also lead to the abrogation of non-renal parameters of harm is of great translational importance. Such alternative therapeutic strategies require further investigation, but it is conceivable that RDN therapy or other experimental strategies to reduce cellular oxygen uptake and rebalance kidney tissue oxygen tension may offer future therapeutic potential. The potential of erythropoiesis-stimulating agents to improve CKD via their EPO-independent renal effects remains to be explored. There is high potential to identify non-hematopoietic EPO targets, which can be modulated by exogenous and potentially also endogenous EPO. Areas of research interest include angiogenesis, fibrosis, mitochondrial biogenesis, and respiration. These fields can give rise to agents for the treatment of comorbid anemia and tissue hypoxia arising from CKD. The investigations into the cardiorenal benefits of currently available cardiovascular agents have so far focused almost exclusively on their blood pressure-lowering effects. Blood pressure-independent potential targets include tissue hypoxia, sodium retention, renal fibrosis, inflammation, uric acid metabolism, and nitric oxide (Humbert et al., 2023). The interaction of hypoxia with fibrosis, inflammation, and mitochondrial metabolism is of high interest. Targeting impaired hypoxia signaling in CKD is also emerging as a potential novel therapeutic approach. These agents and others can be considered for both primary and secondary renal and cardiorenal prevention in CKD.

Conclusion

Finally, treatment with the novel iron-based phosphate binder has been shown to significantly reduce fibroblast growth factor, parathyroid hormone, and other phosphate-induced changes to the myocardium in a rat model of myocardial infarction by reducing the circulating levels of fibroblast growth factor. This potential to reduce cardiovascular morbidity and mortality in this overall complex patient population, with added benefit related to renoprotection and perhaps even to reduce mortality after kidney transplantation, seems fortunate to be an ongoing promise with several novel drugs to come. However, the general requirement for these drugs to be metabolized and excreted via the kidneys may represent an insurmountable obstacle. Additional therapies currently in phase 1–3 clinical trials that have been specifically designed to treat mineral and bone disorders in chronic kidney disease, which I am particularly interested in, will be discussed in more detail. Subcutaneous parathyroid hormone administration with both the full molecule of parathyroid hormone and the carboxy-terminal fragment has been shown to gratifyingly stimulate the endogenous secretion of intact parathyroid hormone, a mechanism that is key to avoiding the excessive stimulus for bone remodeling and rigidity seen with both calcimimetics and vitamin D receptor activators. I believe that these drugs represent the first hope for a truly superior parathyroid hormone replacement therapy. where it stimulates bone formation, there is no increase in serum calcium, unlike the current replacement agents, which have been associated with additional concern for ectopic calcification, as has been the case with active vitamin D. However, the lack of additional actions on calcium balance suggests the absence of these disadvantages. Last but not least, and reassuringly, the lack of excessive bone formation could offer a unique opportunity to treat osteoporosis in chronic kidney disease with a single agent, which would be particularly useful in the immediate post-transplant phase when mineral and bone disorder is crashing immediately to normality, thus exacerbating bone metabolism parameters. The use of non-calcium-based phosphate binders such as lanthanum carbonate and ferric citrate has been an advance in the treatment of hyperphosphatemia, and vitamin D receptor activators can be replaced with D-mimetics, blockers of endocrine FGF23, blockers of the local myocardial FGF23, and blockers of KLOTHO or AKT phosphorylation. However, these new treatments are not without associated risks, and many patients still get overtreated despite the exploitation of these new tools. Encouragingly, there are several new tools on the horizon, such as the use of heparin agents that could prevent uremic injury by interfering with the crystalline structure interaction, the use of pyrophosphate hydrolase, and the use of ectopia sialidase to hydrolyze the sialic acid groups.

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