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Management of chronic kidney disease: The current novel and forgotten therapies

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ABSTRACT

Chronic kidney disease (CKD) is a progressive and incurable condition that imposes a significant burden on an aging society. Although the exact prevalence of this disease is unknown, it is estimated to affect at least 800 million people worldwide. Patients with diabetes or hypertension are at a higher risk of developing chronic kidney damage. As the kidneys play a crucial role in vital physiological processes, damage to these organs can disrupt the balance of water and electrolytes, regulation of blood pressure, elimination of toxins, and metabolism of vitamin D. Early diagnosis is paramount to prevent potential complications. Treatment options such as dietary modifications and medications can help slow disease progression. In our narrative review, we have summarized the available therapeutic options to slow the progression of chronic kidney disease. Many new drug treatments have recently become available, offering a beacon of hope and optimism in CKD management. Nonetheless, disease prevention remains the most critical step in disease management. Given the significant impact of CKD on public health, there is a pressing need for further research. With the development of new technologies and advancements in medical knowledge, we hope to find more effective diagnostic tools and treatments for CKD patients.

Introduction

Chronic kidney disease (CKD) is a prevalent condition that substantially affects both the patient and their immediate surroundings and poses a significant burden on the healthcare system. CKD affects approximately 800 million individuals worldwide [1,2]. Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that glomerular filtration rate (GFR) measurement or estimation is a critical diagnostic tool for CKD [3]. Early diagnosis and management of CKD are crucial to prevent disease progression and minimize the risk of adverse outcomes. Accurate GFR assessment is critical in this regard, as it provides valuable information about the severity and progression of CKD. GFR measurement or estimation is widely recognized as significant in CKD diagnosis and management and is essential in clinical practice guidelines [4]. The five-stage classification system based on GFR levels provides a framework for clinicians to assess CKD severity and tailor management strategies accordingly (Table 1).

Many diseases and potentially toxic damaging agents play a role in CKD development. However, irreversible glomerular and tubular damage develops during CKD pathogenesis, which can be predicted using several biochemical markers [5]. In the initial stage of CKD, albuminuria is the most readily available and best standardized urinary biomarker and is cost-effective with urine dipstick methods. Albuminuria is a predictor of CKD and further increases the cardiovascular risk [4,6]. Therefore, it is recommended that proteinuria levels be divided into stages (Table 2.) Cardiovascular risk also depends on the proteinuria level. Chronic kidney damage can be diagnosed if abnormal kidney function persists for at least three months, as well as in the case of abnormal albuminuria detected despite normal kidney function. CKD is also apparent in structural or morphological abnormalities of the

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Table 1
Stages of chronic kidney disease (CKD) based on estimated glomerular filtration rate (eGFR).

CKD stages	Description	eGFR (ml/min/1.73 m^2)
G1	Mild renal impairment with normal or reduced GFR	>90
G2	Kidney damage, slightly reduced GFR	between 60–89
G3a	Mildly to moderately reduced GFR	between 45–59
G3b	Moderately to severely reduced GFR	between 30–44
G4	Severely decreased GFR	between 15–29
G5	Renal failure	<15 (or renal replacement therapies)

Table 2
Stages of proteinuria. (ACR: albumin/creatinine ratio, TPCR: total protein/creatinine ratio).

Stadiums of albuminuria and proteinuria	Proteinuria (mg/day)		Urine protein/creatinine ratio		Description
	albuminuria	proteinuria	ACR	PCR	
A1	<30	<150	<3	<15	normal/slightly elevated
A2	30–300	150–500	3–30	15–50	moderately increased
A3	>300	>500	>30	>50	increased significantly

kidneys (e.g., polycystic kidney disease in adults) [3].

With advancing age, kidney function can gradually decrease physiologically; the average rate of this is 0.8 ml/min/1.73 m2 per year. However, it does not exceed the decrease in estimated glomerular filtration rate) of 4–5 ml/min per year [7]. Laboratory tests are commonly used to detect reduced kidney function in elderly individuals as this is a natural part of aging. CKD is characterized by scarring of the kidney tissue, leading to a decrease in healthy glomeruli. Along with global glomerulosclerosis, CKD can also damage tubules [8]. A gradual reduction in the number of nephrons has been identified as a significant contributor to the gradual narrowing of the glomerular filtration rate (GFR). The gradual exhaustion of adaptive mechanisms further exacerbates this phenomenon. Activation of the renin-angiotensin system, a key adaptation mechanism, causes systemic and intraglomerular hypertension, ultimately leading to glomerular damage. The oxidative stress that develops as a result of these processes further exacerbates this damage because reactive oxygen free radicals damage the ultrastructural structure. The cumulative effect of these processes eventually triggers a vicious cycle that further impairs kidney function [9,10].

As CKD progresses, the renal function gradually declines. Typical uremic symptoms are observed in patients with severely advanced and untreated kidney damage. Along with the gradual deterioration of kidney function, many accompanying clinical symptoms can be observed as a result of impaired physiological function of the kidneys (Fig. 1.).

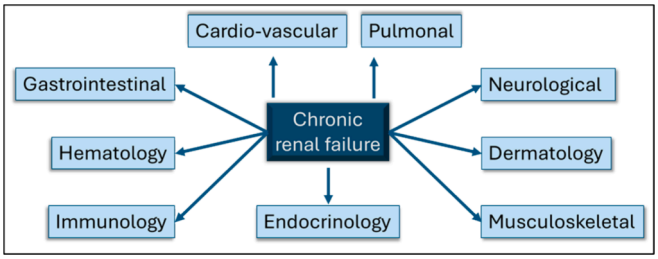

Fig. 1. The decline of kidney function can have an impact on the entire body.

There are many methods for measuring the GFR. In clinical practice, measuring creatinine clearance requires accurate urine 24-hour collection. Creatinine clearance may overestimate the true GFR due to tubular secretion of creatinine. In 2009, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was introduced to estimate the GFR. There are also several inaccuracies in using estimated glomerular filtration rate (eGFR), such as natural GFR narrowing in old age and a significant loss of muscle mass associated with a decrease in serum creatinine level. A significantly reduced muscle mass may overestimate the eGFR [11,12]. In clinical practice, estimating a patient's eGFR based on their serum creatinine levels is possible. However, an alternative method involves determining the serum levels of cystatin C, a marker that is freely filtered through the kidney and is not reabsorbed. The level of cystatin C in the patient's serum is closely correlated with creatinine clearance. In cases where a patient's eGFR value is unrealistically underestimated, and there is no evident kidney damage, the cystatin C level should be determined. This is especially important in cases where chronic kidney disease or albuminuria is suspected, or the patient is predisposed to such conditions. However, it is essential to note that cystatin C determination is unsuitable for use in acute kidney damage, systemic inflammatory conditions, and thyroid disease [13].

The recent introduction of novel drug therapies for chronic kidney disease (CKD) has led to the revision of international recommendations [14]. Our comprehensive narrative review underscores the importance of combining these new pharmacological interventions with established cost-effective and efficacious therapeutic modalities. It is imperative to recognize that a multi-faceted approach to CKD management is essential for optimal patient outcomes.

Materials and methods

Our review delves into current therapeutic procedures for treating chronic kidney disease. Although the latest international professional recommendations emphasize new therapeutic approaches, they do not negate the significance of the established treatment options. Hence, in addition to prevention, it is imperative to consider cost-effective and conveniently accessible treatment options that have demonstrated efficacy in arresting the advancement of chronic kidney disease. In our narrative review, we have provided an overview of the current treatment options. Our intention was not to present a comprehensive summary, as this has been covered extensively in other publications.

Slowing the progression of chronic kidney disease

Nephrological care involves two crucial tasks: preventing chronic kidney disease (CKD) and slowing its progression. Individuals with CKD have a significantly higher risk of morbidity and mortality from cardiovascular disease, regardless of whether they have diabetes or hypertension. Additionally, the risk of death from CKD, particularly from cardiovascular diseases, is higher than that required to start renal replacement therapy [15–17]. Therefore, it is imperative to prevent kidney disease and prevent the progression of CKD. Addressing the underlying conditions that cause CKD is essential to slowing its progression. For instance, treatment of Autosomal Polycystic Kidney Disease (ADPKD), diabetes, hypertension, primary glomerular diseases, and hematological diseases is recommended. The most straightforward approach to slowing kidney disease progression is promptly managing reversible processes, such as possible urine outflow obstruction.

Non-drug treatment options

Therefore, we must use dietary and medicinal options to slow disease progression. The possibility of slowing progression is significantly determined by the underlying disease and the patient's cooperation. Dietary treatment practices are perhaps one of the most important factors in preventing the progression of chronic kidney damage [18]. A

fundamental aspect of maintaining good health is ensuring an adequate daily intake of fluids. It is evident that when one consumes a low amount of fluid, the kidneys need to concentrate the waste, leading to an increased burden when excreting all waste in a single liter of urine compared to three liters. However, avoiding fluid overload is imperative. To establish the amount of fluid required daily, it is most appropriate to ensure that there is no increase in body weight, which can be achieved by consuming an average of 2.0–2.5 L per day. There is ongoing debate concerning the optimal level of dietary protein intake, particularly concerning the reduction and extent of such intake. It is imperative to emphasize that an excessive decrease in protein intake may cause severe malnutrition and loss of muscle mass unless supplemented with ketoacid treatment. In general, it can be posited that clinical studies have demonstrated a reduction in the progression of CKD with a protein intake of 0.8 g/kg body weight/day [19]. The adoption of a low-salt diet not only promotes blood pressure regulation but also mitigates salt-water retention. It is recommended that the daily dietary sodium intake should not surpass 2–3 g or approximately 5 g of table salt. By adhering to this advice, individuals can significantly reduce their risk of developing hypertension and related cardiovascular conditions [18,20–22]. Reducing dietary salt intake does not apply sodium bicarbonate therapy to treat metabolic acidosis. Several published papers have confirmed that the administration of sodium bicarbonate does not significantly affect systemic blood pressure [23–25].

Other important nonpharmacological therapeutic options include a special diet. The first was a plant-based diet, which was an alkaline-rich "alkaline ash" diet. Conventional dietary guidelines for patients with CKD typically prioritize the quantity of nutrients consumed, potentially limiting the intake of fruits and vegetables. This reduction in consumption could result in a loss of opportunity to reap the benefits of higher fiber intake, such as modulation of the gut microbiota to reduce the production of uremic toxins. Additionally, a decrease in the intake of plant fats, such as olive oil, which has anti-atherogenic properties, and plant anions, which may alleviate metabolic acidosis and slow CKD progression, may also occur [26].

Another dietary option is a ketogenic diet. Ketogenic diets (KD) are popular and frequently used for weight loss. These high-fat, low-carbohydrate dietary approaches shift the body into ketosis, where the body primarily relies on fats and ketones for energy instead of carbohydrates. It has been suggested that KD could be considered a new strategy for managing and treating CKD [27].

Perhaps the most logical summarizing diet for healthy choices is the Mediterranean diet. The Mediterranean diet is positively associated with maintaining kidney function, improving the cardiometabolic profile, and reducing mortality risk in individuals diagnosed with CKD. This dietary pattern, characterized by high consumption of plant-based foods, whole grains, fish, and olive oil, and low intake of red and processed meats, has been shown to confer several health benefits. Recent studies have provided evidence of the effectiveness of the Mediterranean diet in managing CKD. Specifically, adherence to this diet is associated with a slower decline in kidney function and a lower risk of progression to end-stage renal disease. Additionally, this dietary pattern has been shown to improve lipid profile, glucose metabolism, and blood pressure in individuals with CKD, thereby reducing the risk of cardiovascular disease. Furthermore, the Mediterranean diet is associated with a lower risk of mortality in individuals with CKD. This is likely due to the beneficial effects of this dietary pattern on several health outcomes, including inflammation, oxidative stress, and endothelial function [28–30].

As CKD advances, the body's uric acid level may increase. Nevertheless, it remains uncertain whether decreasing uric acid levels is effective in slowing the progression of CKD. Therefore, it is advisable to individually determine the treatment for hyperuricemia [31,32].

It is essential to understand that dietary and lifestyle changes should not replace medical treatments but complement them. Each diet has its advantages and disadvantages. To ensure that patients with CKD maximize their health benefits, they should be provided with the necessary knowledge and resources to adopt a diet that best suits their specific needs and CKD stages.

Angiotensin-converting enzyme inhibitors

The benefits of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) in reducing the risk of cardiovascular events (CVEs) and delaying end-stage kidney disease (ESKD) in patients with CKD are well established [33–35]. In cases where contraindications are absent, physicians may elect to use ACEIs in the treatment of hypertension, whereas ARBs are used in cases of intolerance [36]. In CKD, resistant hypertension is common and may necessitate the administration of multiple antihypertensive therapies [37]. For nearly three decades, ACEis and ARBs have been known to reduce urinary protein excretion, exhibit a kidney-protective effect, and effectively slow CKD progression [38]. ACE inhibitors and ARBs not only decrease intra-glomerular pressure but also reduce the amount of primary ultrafiltrate, resulting in a decrease in the reabsorption burden of the tubular epithelium. This includes the fluid volume, electrolytes, and organic substances that need to be reabsorbed by the tubules. It is important to remember that ACEi does not change renal blood flow but improves the medullary blood supply (relatively). Fig. 2 summarizes the main effects of ACEIs/ARBa on kidneys. However, in specific cases, the use of these drugs may result in further deterioration of kidney function and elevated serum potassium levels, leading to the suspension of their use as blood pressure-lowering agents [39–41]. It is important to note that the renal protective effect is only valid in CKD with proteinuria [3].

It is essential to consider whether the use of ACE or ARB inhibitors should be stopped in cases of severe kidney damage. However, the discontinuation of these medications in patients with advanced CKD did not appear to improve kidney function significantly. Instead, it may increase the risk of CVEs and lead to a faster onset of kidney failure [42].

Avoiding nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the production of prostaglandins in the kidneys by paralyzing cyclooxygenase enzymes (COX-1 and COX-2) in the body. This triggers vasoconstriction of the afferent arterioles, leading to worsening intraglomerular blood circulation. NSAIDs also cause salt retention, which can further increase the blood pressure. The long-term use of NSAIDs can cause permanent kidney damage, particularly in older patients. Therefore, the use of NSAIDs is recommended only for acute pathologies and their chronic use

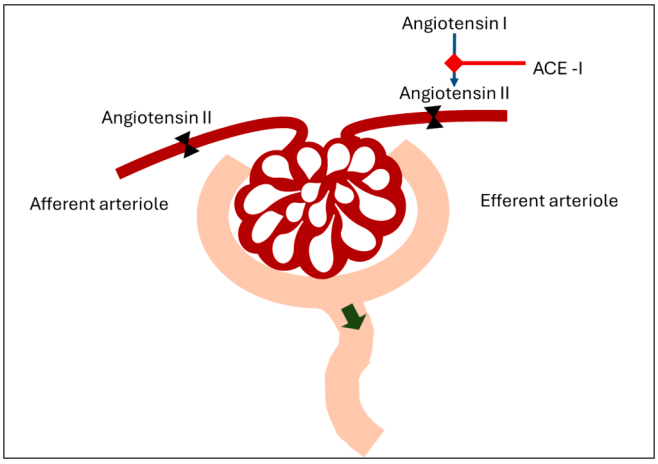

Fig. 2. The already "classic" ACEi/ARB drugs exert their renal protective effect by reducing intraglomerular pressure. Abbreviations: ACE-I: angiotensin convertase enzyme inhibitors.

should be avoided. The cumulative dose determines the complications that develop [43–45]. It is imperative to note that NSAIDs cannot be considered safe in individuals diagnosed with CKD. The use of NSAIDs in patients with CKD has been associated with significant adverse outcomes, such as renal papillary necrosis, acute kidney injury, and chronic kidney disease progression [45]. Therefore, alternative treatments should be considered [46,47].

Use of sodium-glucose cotransporter-2 (SGLT2) inhibitors

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are key therapeutic options for nephrology and CKD treatment. In 2013, the US Food and Drug Administration (FDA) approved this drug for treating type 2 diabetes. These inhibitors are a group of medications used to lower the blood sugar levels. In addition to type 2 diabetes, they are commonly used to treat heart failure [48]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are pharmaceutical agents that inhibit glucose reabsorption in the proximal tubules of the kidneys, resulting in glucosuria (Fig. 3.). Additionally, SGLT2 inhibitors reduce sodium reabsorption, which leads to increased natriuresis and effectively represents a mild add-on diuretic effect [49]. Nevertheless, the entry of sodium into the macula densa was augmented, normalizing the tubuloglomerular feedback. Consequently, vasoconstriction of the afferent arteriole occurs, causing a reduction in intraglomerular pressure [50–52].

These effects provide new opportunities to inhibit the progression of CKD. Since the EMPA-Kidney and DAPA-CKD (EMPA-KIDNEY: Study of Heart and Kidney Protection With Empagliflozin, DAPA-CKD: Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney) studies, we know that SGLT2 inhibitors slow CKD progression even in non-diabetic and patients with proteinuria [3,18,53,54]. Guidelines recommend using SGLT2 inhibitors in patients with CKD with adequate RAAS inhibition based on 1B evidence [3]. The newly proposed KDIGO recommendation advocates the initiation of SGLT2 inhibitors for all CKD patients with an eGFR greater than 20 ml/min without any contraindications. This recommendation is based on the numerous beneficial effects of SGLT2 inhibitors and their potential to improve CKD patients' overall health and well-being. Therefore, healthcare professionals must consider the potential advantages of SGLT2 inhibitors when treating patients with CKD, especially those with a well-preserved eGFR [14].

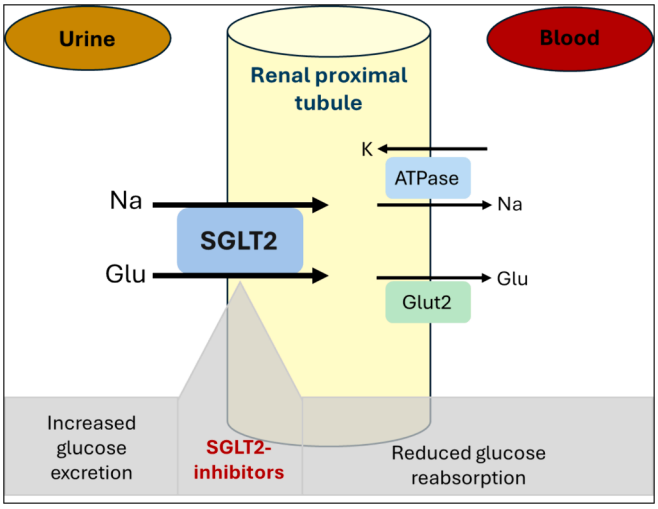

Fig. 3. The main therapeutic effect of SGLT2 inhibitors is the increased excretion of glucose and sodium, which, by starting other physiological processes, we can experience the beneficial effect of such treatment, for example, in heart failure or in slowing down the progression of CKD. Abbreviations: ATPase: Adenosine 5′-TriPhosphatase; Na, natrium; K, potassium; Glu, glucose; Glut2: Glucose transporter 2; SGLT2, sodium/glucose cotransporter 2.

Glucagon-like Peptide-1 (GLP-1) receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists represent a novel class of drugs for treating type 2 diabetes mellitus. These medications exert their pharmacological action by effectively inhibiting incretin production in the small intestine, reducing glucagon secretion and decelerating gastric emptying, ultimately leading to decreased appetite (Fig. 4.) [55]. Notably, GLP-1 receptor agonists have been found to elicit a favorable response in patients with chronic kidney disease (CKD), as evidenced by lowered insulin and glucose levels, as well as moderate blood pressure reduction and hunger [56]. Furthermore, these drugs may be critical in slowing CKD progression by reducing urinary albumin excretion, as observed in clinical studies [57].

According to the SUSTAIN 6 and LEADER clinical trials, GLP-1 receptor agonists exhibit a slower eGFR reduction than placebo controls. This effect was especially pronounced in patients with CKD whose baseline eGFR was less than 60 ml/min/1.73 m2. These findings suggest that GLP-1 receptor agonists may hold promise as therapeutic interventions for patients [18,58]. To date, clinical studies have confirmed the efficacy of GLP-1 analogs solely in patients with diabetes. Nonetheless, the newly released KDIGO recommendations advocate using GLP-1 analogs in the absence of contraindications because of their numerous favorable effects. This recommendation suggests that GLP-1 analogs could be appropriate for a wider range of patients than those with diabetes, promoting a more favorable metabolic environment and weight loss [14,59].

Mineralocorticoid receptor blockade (MRA)

Aldosterone is a steroid hormone that exhibits mineralocorticoid activity. It is synthesized in the zona glomerulosa of the adrenal cortex. Aldosterone facilitates sodium reabsorption in the renal system and promotes potassium excretion in the cortical collecting ducts. Recent studies have suggested that aldosterone and mineralocorticoid activation significantly contribute to the pathophysiology of cardiovascular and renal diseases [60]. The harmful effects of aldosterone on the heart include myocardial hypertrophy, ventricular remodeling, proarrhythmic effects, myocardial ischemia, and reduced blood flow in the coronary arteries (Fig. 5.). Aldosterone in the renal system may cause glomerular hypertrophy, glomerulosclerosis, proteinuria, and consequent kidney damage [61–63].

Adding aldosterone antagonists to ACEi/ARBs to reduce CKD progression can further reduce proteinuria; however, this also increases the risk of hyperkalemia. Patients who experience mild hyperkalemia due to ACEi/ARB use may concurrently present with mild metabolic acidosis known as non-anion gap metabolic acidosis (NAGMA). Therefore, these patients are potential candidates for NaHCO3 supplementation. Empirical evidence suggests that adding NaHCO3 can effectively ameliorate and reverse hyperkalemia. In contrast, nonsteroidal mineralocorticoid receptor blockers are more efficient and selective in reducing proteinuria and have a lower risk of hyperkalemia. Finerenone is a nonsteroidal MRA that reduces albuminuria and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and does not cause hyperkalemia [18,64].

Treatment of metabolic acidosis

As chronic kidney disease (CKD) progresses, renal function declines, reducing the ability of the body to excrete H + and reabsorb bicarbonate. This results in metabolic acidosis, which can lead to further cellular damage (Fig. 6) [65]. Metabolic disturbances are key contributors to the incidence of non-anion gap metabolic acidosis (NAGMA) in patients diagnosed with CKD. Specifically, decreased renal acid excretion, increased ammonia generation, and bicarbonate loss are notable factors. However, it is important to note that the source of NAGMA in CKD is not related to the factors mentioned earlier but rather to other metabolic processes. Fortunately, research has found that administering oral

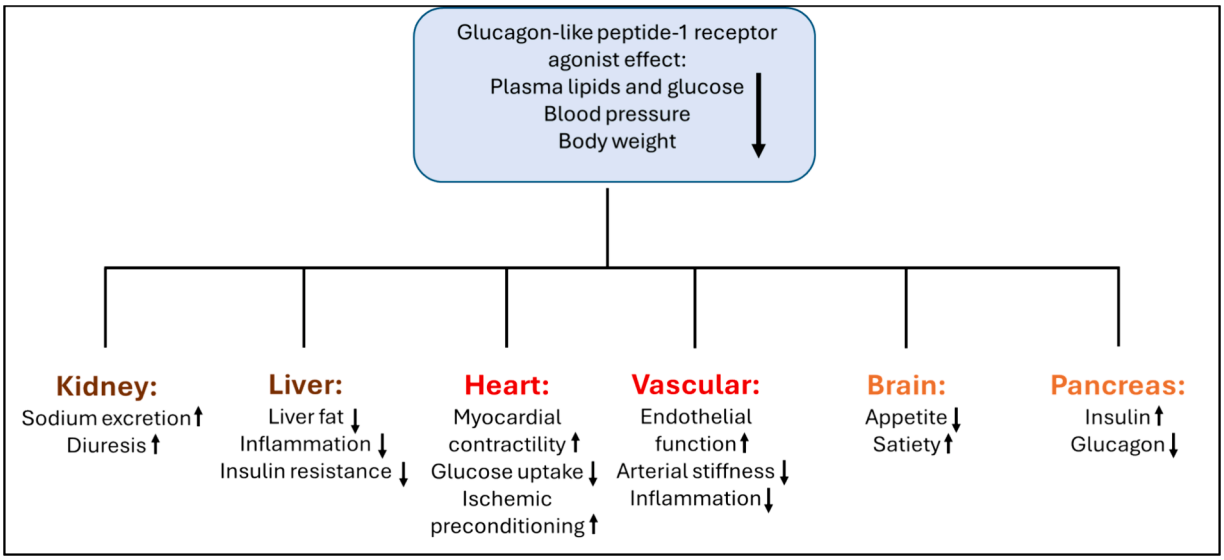

Fig. 4. The use of GLP-1 analogs appears to have many other beneficial effects in addition to treating diabetes.

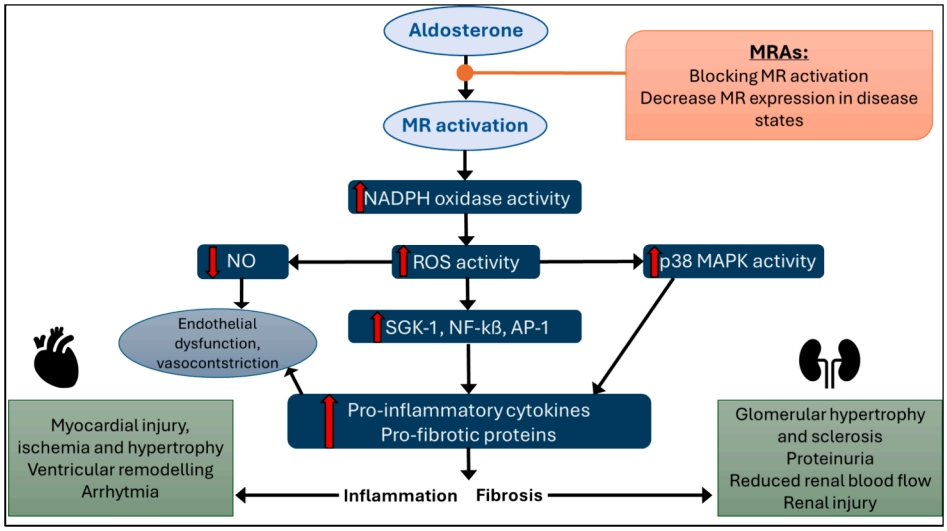

Fig. 5. The amelioration of aldosterone activity by reducing or inhibiting its function is highly beneficial to the cardiovascular system. In addition, it is an effective measure for slowing the progression of chronic kidney disease (CKD). Abbreviations: AP-1: Activator protein 1; MRA, mineralocorticoid receptor antagonist; NO, nitrogen monoxide; NADPH, nicotinamide adenine dinucleotide phosphate oxidase; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; ROS: Reactive oxygen species; SGK-1: Serine/threonine-protein kinase.

sodium bicarbonate is a straightforward and cost-effective method to slow the progression of CKD [66–68].

A method of providing a base and/or reducing dietary acid load can be implemented to treat metabolic acidosis and reduce its harmful effects. The latest recommendations suggest initiating base treatment when serum bicarbonate levels fall below or equal to 24 mEq/L to maintain total CO2 levels between 24 and 26 mEq/L [69]. The extent to which urinary acidification cessation could represent an endpoint for CKD-controlling intervention methods aimed at prolonging renal survival is indeterminate.

Use of Pentoxifylline

Although Pentoxifylline is no longer frequently used, it has been shown to decelerate CKD progression. Pentoxifylline (PTF) is a methylxanthine derivative and non-specific phosphodiesterase inhibitor. Its mode of action involves the inhibition of cyclic-30,50-phosphodiesterase (PDE), which results in an elevation in the intracellular concentration of cyclic adenosine monophosphate (cAMP) and the consequent activation of protein kinase A (PKA) [70,71]. This, in turn, enhances the microcirculation and induces potent hematopoietic properties. Pentoxifylline is known for its potent antiproliferative and anti-inflammatory properties, making it a highly beneficial medication. It is frequently prescribed to treat peripheral vascular diseases and CKD [72,73]. The recommended oral dose is 400 mg, administered twice or thrice daily with a meal. However, the specific dosage may vary depending on an individual's medical needs. In 2012, a study was conducted to examine the effects of a specific medication on 91 patients over one year. The findings revealed that the drug successfully lowered the levels of high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor α (TNF-α), and fibrinogen in the blood [71]. Furthermore, it was observed that the eGFR increased by 2.4 mL/min/1.73 m2. Other studies have also indicated that this medication, PTF, improves kidney function in individuals with CKD and reduces proteinuria [74].

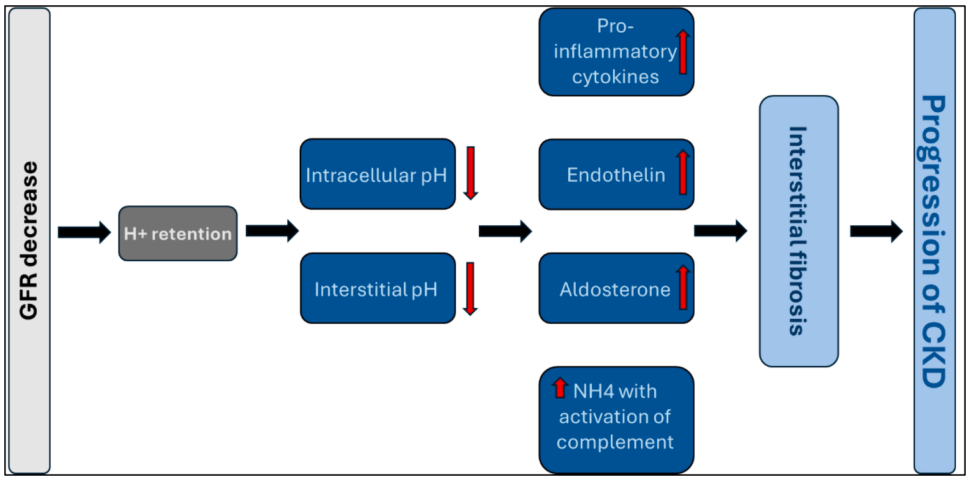

Fig. 6. Treating metabolic acidosis is a cost-effective and straightforward approach. Importantly, correcting metabolic acidosis has been shown to decelerate the progression of chronic kidney disease (CKD), emphasizing the significance of this clinical intervention. Abbreviations: CKD: chronic kidney disease; GFR: glomerular filtration rate; NH4: Ammonium.

Treatment of renal anemia

Renal anemia can occur in the early stages of CKD (stage 3a). Anemia leads to tissue hypoxia, contributing to further progression [75]. It is plausible that ameliorating anemia would improve oxygen delivery to the medulla. Renal anemia is caused by reduced erythropoietin production [76]. A diagnosis can be made if other causes, such as iron deficiency, are ruled out [77,78]. If the patient's hemoglobin concentration is consistently below 11 g/dl (Htc < 0.33 %) and secondary causes of anemia can be ruled out, erythropoietin treatment should be initiated [3]. In contemporary medical practice, a wide range of medications are available to stimulate the production of red blood cells [79]. Human recombinant erythropoietin products are among these drugs. Hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) agents are currently available for this purpose. These agents function by inhibiting the activity of hypoxia-inducible factor prolyl hydroxylase enzymes, leading to reversible inhibition that mimics the natural response of the body to hypoxia. As a result, the body's natural process of red blood cell formation is activated [80]. It must be noted that these drugs are currently only accessible to dialysis patients [81] (e.g., Daprodustat, Vadadustat, Roxadustat) [82]. Normalization of the patient's blood count is not recommended; the target hemoglobin range to be achieved is–11–12 g/dl. In addition to erythropoietin treatment, the body's iron supply must be regularly monitored [3,18,83]. In some cases, erythropoietin resistance may develop after erythropoietin treatment. In such cases, we must rule out additional folic acid and vitamin B12 deficiencies in addition to possible iron deficiency. Uncorrected metabolic acidosis, chronic infections, and secondary hyperparathyroidism are the most common causes of erythropoietin resistance in patients with CKD.

Ckd-metabolic bone disease

Hyperphosphatemia is a common complication of chronic kidney disease (CKD). Phosphate retention begins in the early stages of CKD and contributes to the development of secondary hyperparathyroidism. Properly regulating mineral and bone metabolism relies on the function of various hormones that oversee the calcium and phosphate levels (Fig. 7.). These hormones consist of parathyroid hormone (PTH), calcidiol or 25 (OH)D3 (which is the precursor of calcitriol), calcitriol or 1,25 (OH)2D3 (the most potent form of the vitamin D hormone system), calcitonin, and FGF23/klotho.

These hormones play a significant role in maintaining bone health and metabolism. CKD can significantly alter various body parameters,

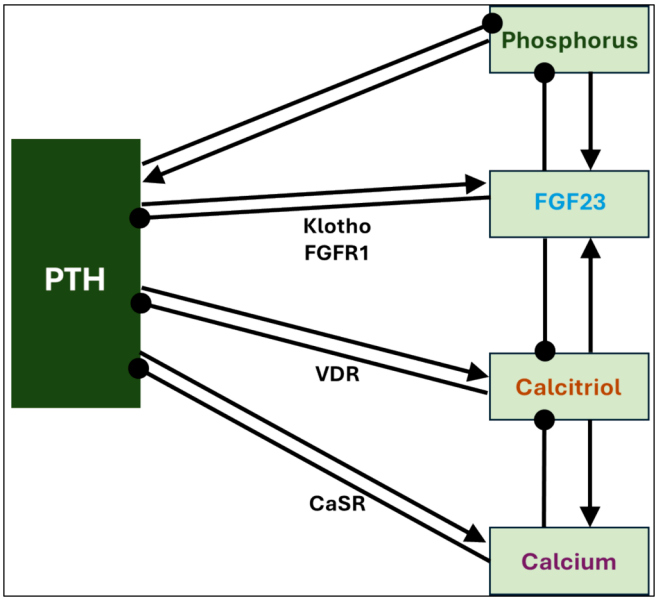

Fig. 7. Metabolic bone disease in chronic kidney disease (CKD) is a multifaceted autoregulatory disorder. Interventions must be enacted at several key points to address this condition. Treating metabolic bone disease in CKD necessitates a comprehensive approach that targets the underlying mechanisms contributing to the disease. Appropriate management of this complex condition requires a thorough understanding of the pathophysiological processes underlying metabolic bone disease in CKD. Abbreviations: PTH: parathyroid hormone; VDR: vitamin D receptor; FGFR1: Fibroblast growth factor receptor 1; FGF23: Fibroblast growth factor 23.

including calcium, phosphate, PTH, FGF23/Klotho, and the vitamin D hormonal system, encompassing calcidiol and calcitriol. These changes can affect bone and vascular metabolism, ultimately leading to adverse clinical outcomes such as decreased bone mass, increased fragility fractures, and vascular and valvular calcification [84]. Patients with CKD often experience disruptions in the regulation of healthy bone turnover. Achieving optimal laboratory values is essential for managing this condition and can be determined based on published results. For patients undergoing hemodialysis, the recommended laboratory ranges are phosphate levels between 3.6 to 5.2 mg/dl, calcium levels between 7.9 to 9.5 mg/dl, and parathyroid hormone (PTH) levels between 168 to

764 pg/ml. Notably, in hemodialysis, PTH levels are typically 2–9 times higher than the normal range [85].

In the case of a significant decrease in GFR, a bone density test alone is not sufficient to assess bone metabolism because it cannot differentiate between the bone metabolism differences characteristic of various kidney diseases, such as adynamic bone disease, osteitis fibrosa caused by secondary hyperparathyroidism, or osteomalacia. However, the assessment of bone metabolism in patients with early CKD (stages 1–2) is similar to that in a healthy population [86]. Starting with CKD stage 3a, calcium, phosphorus, alkaline phosphatase, parathyroid hormone, and 25-hydroxyvitamin D levels are recommended every 3–6 months [87]. Additional treatment options for bone and mineral metabolism disorders accompanying kidney disease include native vitamin D supplementation, active vitamin D/vitamin D receptor agonists (e.g., paricalcitol), and calcimimetic drugs (e.g., cinacalcet, etelcalcetide) applications [3,88,89]. Parathyroid resection may be considered an alternative treatment option when there is insufficient medical intervention. Research has demonstrated that this surgical procedure yields favorable long-term outcomes [90]. A new biological treatment offers hope for CKD-MBD treatment, particularly in osteoporosis patients. Denosumab is a receptor activator of nuclear factor-κB ligand (RANK-L) inhibitor that reduces bone resorption, impairs osteoclast formation and function, and increases bone mineral density. This novel treatment is particularly promising because it targets the underlying mechanisms of CKD-MBD, which can lead to serious complications, such as bone fractures and cardiovascular disease. By inhibiting RANK-L, denosumab effectively reduced the risk of these complications and improved patients' quality of life with CKD-MBD. As a result, this treatment has the potential to become a valuable addition to the current treatment options for CKD-MBD, offering a safe and effective alternative for patients who cannot tolerate other forms of treatment [91–93].

Conclusions

In summary, timely recognition of chronic kidney damage is important for slowing down the progression and treating additional complications that develop in parallel with chronic kidney damage. Previously, only ACEI or ARB preparations could be used for kidney protection; non-steroidal MRAs, SGLT2 inhibitors, and GLP1 receptor agonists can also be used to slow the progression of chronic kidney disease. Cardiovascular death can also be reduced by treating the associated complications. In addition to drug treatment, the revision of dietary habits is helpful. The dosage of certain drugs must be adjusted in parallel with the reduction in kidney function. Prevention of CKD development of chronic kidney disease is vital. The treatment of chronic kidney disease requires a complex approach. If, despite therapeutic attempts, the progression of kidney disease cannot be slowed, such a patient must be prepared in time for kidney replacement treatment or, if suitable, placed on the kidney transplant waiting list.

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Declaration of competing interest

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