

CARDIOVASCULAR RISK FACTORS IN CHRONIC KIDNEY DISEASE PATIENTS ON RENAL REPLACEMENT THERAPY

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Cardiovascular disease (CVD) remains the leading cause of mortality in patients with end-stage renal disease (ESRD). The risk factors for CVD in this population can be categorized into three main groups: traditional (non-modifiable factors such as male gender, age over 65 years in men and over 75 years in women, and a family history of cardiovascular disease; modifiable factors encompass hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, and physical inactivity), renal-specific (anemia, chronic fluid overload, mineral and bone disorders, chronic inflammation, electrolyte imbalances, and oxidative stress), and transplant-specific (immunosuppressive therapy and graft dysfunction). Risk factors related to renal pathology and immunosuppressive therapy following kidney transplantation play a role comparable in significance to traditional CVD risk factors. Early detection and management of these factors are critical for reducing CVD incidence in this patient population.

Keywords: cardiovascular disease, cardiovascular risk factors, chronic kidney disease, end-stage renal disease, dialysis.

INTRODUCTION

Chronic kidney disease (CKD) has emerged as a major global health problem, reaching pandemic proportions in recent decades. It is estimated that more than 850 million people, approximately 10% of the world's population, are affected by CKD, a figure that is twice the global prevalence of diabetes [1].

The number of patients progressing to end-stage renal disease (ESRD) and requiring renal replacement therapy (RRT) is also steadily rising, with estimates ranging from 4.9 to 7.1 million worldwide [2]. A similar trend is observed in Russia. According to the Russian RRT Registry, 24,195 patients (170.5 per million population) were receiving RRT in 2009 [3]; by 2024, this number had increased more than threefold to 74,238 (499 per million population) [4].

Although kidney transplantation (KT) offers better survival rates and quality of life compared to dialysis, approximately 80% of patients with ESRD remain on dialysis due to the persistent shortage of donor organs. In 2023, a total of 111,135 kidney transplants were performed worldwide [5], including 1,817 in the Russian Federation [6]. By early 2025, 15,240 patients in Russia were living with functioning kidney transplants [4].

Cardiovascular disease (CVD) remains the leading cause of death among patients with CKD, particularly those with kidney failure [7]. Cardiovascular risk factors in this population can be grouped into three categories: traditional [8], renal-specific, and transplant-specific factors (Table 1).

Table 1

CVD risk factors in ESRD patients

Traditional CVD risk factors [8]	Non-modifiable: – Male gender – Age: high 10-year cardiovascular risk in men over 65 years and women over 75 years – Family history Modifiable: – Hypertension (HT) – Diabetes mellitus (DM) – Dyslipidemia – Smoking – Obesity – Sedentary lifestyle
“Renal” CVD risk factors	– Anemia – Chronic hyperhydration – Mineral and bone disorders – Chronic inflammation – Electrolyte disturbances – Oxidative stress
Post-kidney transplant CVD risk factors	– Immunosuppressive therapy – Transplanted kidney dysfunction

CVD RISK FACTORS IN ESRD

Given that traditional CVD risk factors in patients with kidney failure are similar to those observed in the general population and are widely discussed in the literature [8], this paper focuses on “renal” factors and factors specific to patients following KT.

Anemia

Anemia is one of the most common complications of CKD, resulting from decreased erythropoietin production, shortened red blood cell lifespan, and other factors. As a recognized risk factor for CVD, anemia contributes to morphological and functional cardiac changes, including left ventricular (LV) hypertrophy and dilatation, diastolic dysfunction, arrhythmias, and heart failure (HF) [9].

The international DOPPS study reported that approximately 47% of dialysis patients had hemoglobin (Hb) levels below 110 g/L, while 84% were receiving erythropoietin (EPO) therapy. Importantly, Hb concentrations in the range of 110–120 g/L were associated with lower mortality and hospitalization rates [10].

At the same time, it has been shown that increasing Hb levels to higher values (≥ 135 g/L) is associated with a greater risk of composite cardiovascular complications [11]. Specifically, the use of EPO preparations to achieve Hb concentrations of ~ 130 g/L was linked to an increased incidence of stroke, more aggressive hypertension, and vascular access thrombosis compared with achieving levels of ~ 101 g/L [12].

According to the KDOQI and KDIGO clinical practice guidelines, EPO therapy may be initiated when Hb levels fall within 90–100 g/L, to prevent further decline below 90 g/L. However, it is not recommended to use EPO to maintain Hb levels above 115 g/L or to deliberately raise them above 130 g/L [13, 14]. Importantly, target Hb levels should be individualized and guided by the patient's clinical status and comorbid conditions. The Russian Ministry of Health has adopted a similar approach in its recommendations for the management of anemia in CKD [15]. The main goal of using EPO preparations is to reduce the need for blood transfusions [9].

After KT, anemia is observed in 20–60% of patients, most is in the early post-transplant period (within the

first 2 months after surgery) [16]. The main causes of post-transplant anemia are summarized in Table 2 [17].

Post-transplant anemia, defined as Hb levels below 110 g/L at 3 months after KT, is associated with adverse outcomes, including congestive heart failure, poorer graft and patient survival, and a higher incidence of acute rejection [18].

In kidney transplant recipients, treatment should be initiated with EPO when Hb falls below 110 g/L, with the therapeutic goal of maintaining Hb in the range of 110–120 g/L [16].

Chronic overhydration

Overhydration represents a major pathogenetic factor contributing to CKD progression and unfavorable outcomes. Multiple observational studies have shown that chronic fluid overload in dialysis patients significantly increases the risk of both all-cause mortality and CVD [19, 20].

A major challenge in both clinical practice and research is the quantitative assessment of hyperhydration in individual patients. This challenge has been partly addressed by the widespread adoption of Bioelectrical impedance analysis (BIA), which enables the assessment of total body fluid volume as well as the distribution of intracellular and extracellular fluid [21, 22]. Today, BIA techniques are routinely used in most modern studies on hydration.

Hyperhydration has been shown to be strongly associated with left ventricular hypertrophy (LVH) [23] and increased mortality, [24] even in the pre-dialysis stages of CKD, regardless of disease severity. Among patients with stage 4–5 CKD, overhydration is linked not only to higher mortality but also to a greater incidence of CVD [25].

Evidence from several meta-analyses confirms that hyperhydration in ESRD patients receiving RRT is an independent predictor of all-cause mortality, as well as a risk factor for cardiovascular complications and mortality [26–28]. Numerous studies further demonstrate associations between hyperhydration and LVH, diastolic dysfunction, reduced cardiac output, endothelial dysfunction, increased arterial stiffness [29, 30], and chronic systemic inflammation [31]. Even after adjusting for confounding variables and in the absence of overt cardiovascular pathology, hyperhydration remains an independent risk factor that worsens prognosis in patients with ESRD.

This dependence is observed in patients undergoing peritoneal dialysis (PD) [32], as well as in those on hemodialysis (HD) [33].

In PD patients, hyperhydration is predominantly persistent, often resulting from inaccurate assessment of “dry weight” or inadequate ultrafiltration volume. Patients receiving maintenance HD may experience a combination of both persistent and intermittent hyperhy-

Table 2

Main causes of anemia in patients after kidney transplantation [17]

In the early post-transplant period
– Perioperative blood loss
– Discontinuation of erythropoietin (EPO) therapy
– Iron deficiency
– Bone marrow suppression associated with induction immunosuppressive therapy
– EPO resistance, triggered by ongoing infections, inflammatory processes, or the use of certain medications (e.g., mycophenolate mofetil)
In the late post-transplant period
– Decreased endogenous erythropoietin production due to allograft dysfunction
– EPO resistance associated with secondary hyperparathyroidism
– Chronic inflammatory conditions

dration. Persistent hyperhydration is generally absent if fluid status is correctly assessed in these patients. However, because most HD patients have almost complete loss of renal function, including the ability to excrete water, fluid intake accumulates between sessions. The most pronounced cardiovascular system (CVS) changes are typically observed at the end of the three-day interdialysis interval, when intermittent hyperhydration reaches its peak [34, 35].

Studies indicate that exceeding a threshold of interdialytic weight gain – typically estimated at 15% of extracellular fluid volume – is strongly associated with increased mortality [36]. With fixed dialysis session durations, excessive weight gain necessitates higher ultrafiltration rates, which further elevate mortality risk [37]. Rapid volumetric ultrafiltration, even in the absence of overt complications such as intradialytic hypotension, can induce myocardial “stunning”, characterized by regional hypokinesia, and, with prolonged exposure, may progress to systolic dysfunction, heart failure, and increased mortality [38, 39].

Minimizing intermittent hyperhydration is therefore closely linked to optimizing sodium balance in patients on maintenance HD. This is achieved through a combination of dietary sodium restriction and individualized adjustment of dialysate composition [40].

Over the past decade, lung ultrasound has been increasingly studied as a tool for assessing hydration status in dialysis patients. An increase in pulmonary interstitial water content produces characteristic artifacts known as “comets” or B-lines [41]. Several studies have reported

a correlation between the number of B-lines and clinical outcomes in HD patients [42]. However, lung ultrasound findings often do not align with BIA results. This discrepancy may be explained by the fact that BIA measures total extracellular fluid without distinguishing between interstitial and intravascular compartments, whereas B-lines may also be influenced by left ventricular dysfunction and pulmonary congestion [43, 44]. In other words, BIA provides a broader estimate of hydration status, while lung ultrasound is more closely associated with intravascular volume. Given its accessibility and non-invasive nature, lung ultrasound merits further investigation and may ultimately become a standard tool in routine clinical practice.

Hyperhydration is one of the most critical factors contributing to cardiovascular pathology and reduced survival in patients with kidney failure. Addressing both persistent and intermittent hyperhydration remains a major challenge, as it requires reliable methods for assessing hydration status, minimizing interdialytic weight gain in patients on long-term HD, and ensuring safe ultrafiltration – all of which demand further research and the development of effective therapeutic strategies.

Mineral and bone disorders

The kidneys play a central role in mineral and bone metabolism (Fig. 1). Current evidence suggests that a reduction in the functional nephron mass and progression of CKD initially disrupt vitamin D metabolism, resulting in hypocalcemia and hyperphosphatemia [45]. In addition, reduced expression of the α -klotho gene

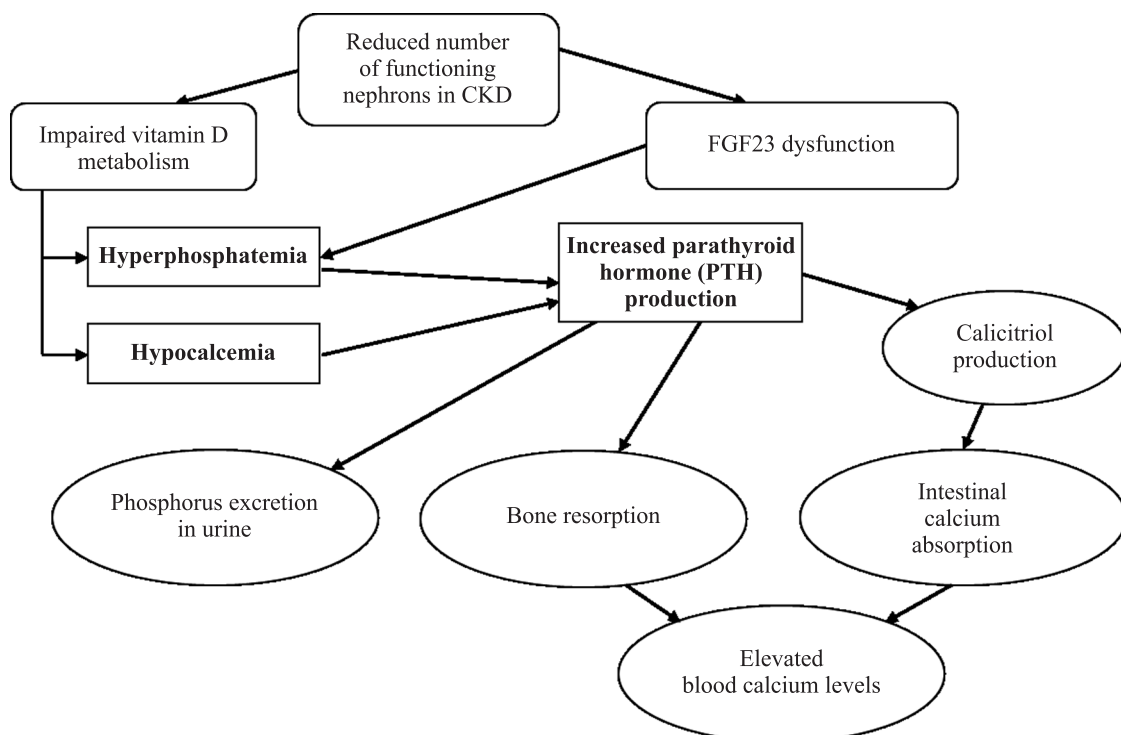


Fig. 1. Mineral and bone disorders in CKD

in distal renal tubules impairs the activity of fibroblast growth factor 23 (FGF23) as a phosphaturic hormone, ultimately leading to the retention of inorganic phosphate in the body [46].

As a compensatory response, FGF23 production increases in bone tissue, followed by suppression of 25-hydroxyvitamin D hydroxylase activity, thereby reducing calcitriol synthesis and stimulating parathyroid hormone (PTH) secretion [47].

The combined effects of FGF23 and PTH inhibit phosphate reabsorption in the proximal tubules, enhancing urinary phosphate excretion. In addition, PTH promotes bone resorption and sustains calcitriol production, which facilitates intestinal calcium absorption and contributes to the maintenance of normal serum calcium levels [48].

With progressive loss of kidney tissue, these compensatory mechanisms become ineffective, resulting in mineral and bone disorders characteristic of ESRD, which exert profound pathological effects on CVS. Numerous studies have reported that hyperphosphatemia is strongly associated with an increased risk of adverse cardiovascular outcomes, including myocardial infarction, stroke, heart failure, sudden cardiac death, and peripheral arterial disease [49, 50]. Hyperphosphatemia contributes to endothelial dysfunction and promotes vascular and valvular calcification [51]. It also stimulates elevated PTH levels, which are linked to increased cardiovascular mortality [52]. Similarly, elevated FGF23 levels are associated with higher cardiovascular morbidity and mortality in CKD patients. Both PTH and FGF23 are believed to exert direct effects on cardiomyocytes, triggering LVH [53].

Hypocalcemia, a hallmark of mineral and bone metabolism disorders in CKD, is linked to arterial hypotension, congestive heart failure, and cardiac arrhythmias. It is also associated with QT interval prolongation, which increases the risk of ventricular tachycardia and ventricular fibrillation [54, 55]. At the same time, CKD patients may develop excessive calcium overload, particularly when treated with calcium-containing phosphate binders and active vitamin D analogues. This condition accelerates the formation and maturation of calciprotein particles, thereby promoting vascular and valvular calcification and advancing atherosclerosis. Ectopic calcification within the cardiac conduction system further elevates the risk of fatal bradyarrhythmias [56].

In severe renal failure, expression of the α -klotho gene and synthesis of calcitriol, both of which exert cardioprotective effects, are reduced [57, 58]. Moreover, CKD is often associated with magnesium deficiency, despite evidence suggesting that adequate magnesium levels may slow or even halt CVS calcification processes [59].

Extracartilaginous calcification affecting the CVS is the main manifestation of mineral and bone disorders in CKD and is a major determinant of the elevated morta-

lity risk in CKD [60]. Calcification primarily affects the medial layer of arterial walls and the cardiac valves. The underlying mechanism is thought to involve the formation of calcium-phosphorus particles containing fetuin-1 and other proteins, which induce vascular smooth muscle cells to undergo phenotypic transformation into osteoblast-like cells capable of producing bone matrix within the vessel wall [61]. These particles also stimulate the release of pro-inflammatory cytokines, further amplifying the calcification process [51].

Current therapeutic approaches to mineral and bone disorders in CKD focus on achieving recommended target levels of key modulators of mineral metabolism. A variety of agents have been employed, including phosphate binders, vitamin D analogs (both native and active forms), calcimimetics, and bisphosphonates [62]. While these treatments are effective in correcting biochemical parameters, they have not shown sufficient impact on overall or cardiovascular mortality [62, 63]. Thus, although the association between disordered mineral metabolism in kidney failure and cardiovascular mortality is well established by cohort studies, pharmacological correction of these disturbances has yet to translate into improved clinical outcomes [63].

Inflammation

The progression of CKD is closely linked to systemic inflammation and oxidative stress, which contribute to a wide range of complications, including malnutrition, atherosclerosis, vascular calcification, heart failure, anemia, mineral and bone disorders, and increased cardiovascular mortality. Declining renal function leads to accumulation of advanced glycation end products and pro-oxidants, which promote oxidative damage, activate mononuclear cells, and stimulate chronic inflammatory pathways [64].

In patients with kidney failure, elevated levels of pro-inflammatory cytokines result not only from increased production but also from impaired clearance. The uremic state itself, together with comorbid conditions, genetic predisposition, and lifestyle factors, sustains a subacute inflammatory response. Additional dialysis-related factors further exacerbate inflammation, including the use of central venous catheters (CVCs), repeated contact of blood with dialysis membranes and extracorporeal circuit components, potential contamination of dialysate with bacterial endotoxins and backfiltration in the dialyzer, as well as infections such as catheter-related bacteremia and peritonitis in PD (Fig. 2) [65].

There is a clear positive correlation between creatinine clearance and concentrations of various pro-inflammatory cytokines, particularly interleukin (IL)-6, across different stages of CKD. Durlacher-Betzer et al. demonstrated that IL-6 plays a key role in stimulating FGF23 expression in uremia, with elevated FGF23 levels strongly associated with increased mortality [66].

Chronic hyperhydration, frequently observed in ESRD patients, further contributes to systemic inflammation. Intestinal wall edema promotes bacterial translocation and endotoxin leakage, which in turn activate the immune system and amplify cytokine production. Moreover, reduced renal clearance shifts the excretion of urea to the intestinal microbiota, leading to increased ammonium hydroxide formation and elevated intestinal pH. These changes disrupt the normal gut microbiome, favoring the growth of pathogenic species that drive persistent inflammatory processes [67].

Lipopolysaccharide-binding protein (LBP) is an acute-phase reactant that mediates immune responses triggered by microbial products. In patients undergoing maintenance HD, Paik Seong Lim et al. reported a significant positive correlation between circulating LBP levels and markers of systemic inflammation such as C-reactive protein (CRP), IL-6, and soluble CD14 [68]. Moreover, serum LBP level has been shown to independently predict the risk of cardiovascular events in this patient population, underscoring its role as both a biomarker and potential mediator of inflammation-driven cardiovascular injury [69].

Comorbidities such as congestive heart failure, diabetes, hypertension, and age-related changes in the immune response contribute to the development of chronic

inflammation [70]. Patients with diabetes have elevated plasma levels of IL-1, IL-6, IL-18, tumor necrosis factor- α (TNF- α), ICAM-1, VCAM-1, and NF- κ B [71]. Hypertension is associated with increased IL-6, VCAM and ICAM-1 levels [72]. Similarly, obesity drives the upregulation of IL-18, IL-1 β , and TNF- α [73]. Acute and chronic infections, in particular periodontitis [74], viral hepatitis, and peritonitis in patients on peritoneal dialysis [75], play a separate role in stimulating the inflammatory response.

The pathophysiology of inflammation may vary among CKD patients depending on their genetic background. Losito et al. demonstrated a link between the IL-6-174G/C promoter polymorphism, arterial hypertension, and LVH in hemodialysis patients, particularly in those with diabetes [76]. Subsequently, Sharma et al. reported a link between polymorphisms in the promoter regions of proinflammatory cytokines (IL-6, TNF- α) and the regulatory monokine IL-10 with the development of ESRD, malnutrition-inflammation syndrome, comorbidities, and increased mortality risk in patients on maintenance hemodialysis [77].

Several studies have shown that vascular calcification is present in 30–70% of adult patients with CKD [78] and in nearly 15% of children with uremia [79]. ESRD patients are characterized by increased arterial stiffness,

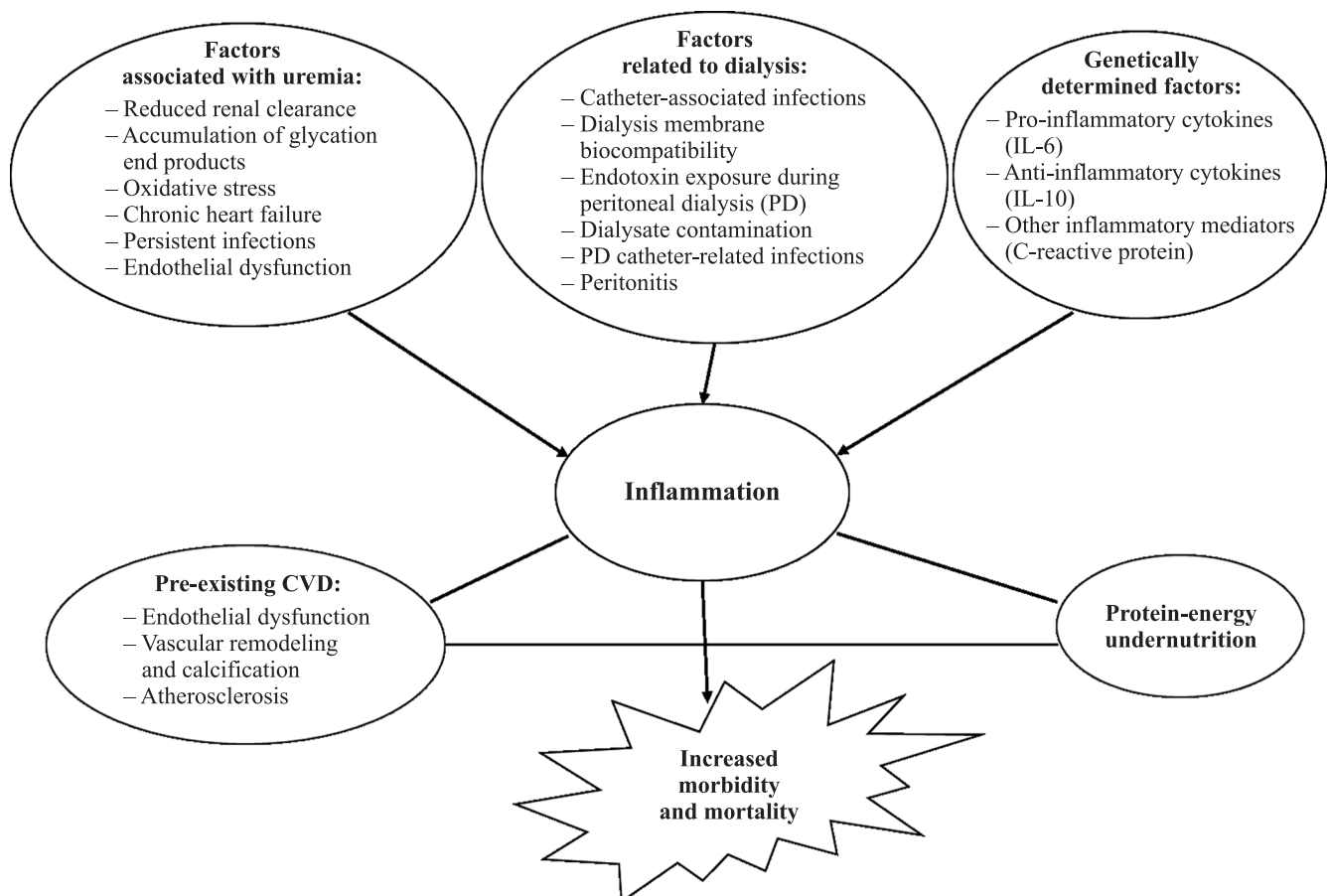


Fig. 2. Causes and consequences of inflammation in ESRD patients. Adapted from [65]

particularly in the aorta, common carotid artery, and cerebral vessels [80]. In addition, they frequently exhibit arterial dysfunction manifested by impaired nitric oxide-dependent vasodilation [81] and elevated pulse wave velocity [82].

Inflammatory cells accumulate within developing atherosclerotic plaques and in the aortic valve, underscoring the close link between systemic inflammation and vascular calcification. This process arises from deposition of calcium phosphate crystals in the arterial intima, resembling the mineralization seen in bone tissue. Nadra et al. [83] demonstrated that human macrophages exposed to calcium phosphate crystals *in vitro* internalize these crystals into vacuoles and subsequently release inflammatory cytokines (TNF- α , IL-1 β , IL-8) through a protein kinase C-dependent mechanism. In addition, macrophages are able to secrete matrix vesicles enriched with annexin V and alkaline phosphatase, which possess strong calcifying potential [84]. The receptor activator of NF- κ B ligand (RANKL) is a membrane-bound or soluble cytokine necessary for osteoclast differentiation, whereas osteoprotegerin masks the activity of RANKL. It can stimulate inflammation in atherosclerotic plaques, which in turn contributes to the further progression and complications of atherosclerosis, indicating a vicious circle of interrelated processes: inflammation and calcification of the arteries [85].

Fetuin-A, a glycoprotein of approximately 60 kDa synthesized by hepatocytes, is the most potent circulating inhibitor of calcification, preventing hydroxyapatite formation. Elevated levels of proinflammatory molecules can suppress fetuin-A production, leading to reduced serum levels, which are associated with increased cardiovascular risk and poorer outcomes in patients with CKD [86].

A substantial body of evidence highlights the role of inflammation in atherogenesis, demonstrating that the relationship between inflammation and CVD is evident not only in patients with renal failure but also in the general population [87]. For example, the JUPITER study showed that lowering high-sensitivity C-reactive protein (hs-CRP) levels with rosuvastatin significantly reduced the risk of cardiovascular complications, even in individuals with normal cholesterol levels [88]. Nishi et al. reported that pentraxin 3, hs-CRP, and tumor necrosis factor- α (TNF- α) were significantly elevated in patients with CKD and concomitant CVD compared to those without CVD. Jia Sun et al. identified circulating IL-6 and VCAM-1 as independent predictors of cardiovascular events and all-cause mortality in patients on maintenance HD [89].

All these studies demonstrate an undeniable link between inflammation and CVD in CKD patients. Following KT, restoration of renal function leads to significant changes in several inflammatory markers, which in turn influences cardiovascular risk. Yilmaz M.I. et al.

reported that after transplantation, reductions in CRP and FGF23 levels were accompanied by a marked decrease in carotid intima-media thickness (-22% , 95% CI -24 to -20% , $p = 0.001$) [90]. A two-year study by Kensinger C. et al. showed that endothelial function improves after transplantation and remains stable for at least two years postoperatively [91].

Oxidative stress

Increased oxidative stress is closely associated with a higher risk of CVD in patients with kidney failure. Since the kidneys are one of the main sources of antioxidant enzymes, including glutathione peroxidase, their damage in ESRD leads to a reduction in these enzymes and a concomitant rise in prooxidants. Uremic toxins further contribute by activating polymorphonuclear leukocytes, monocytes/macrophages, lymphocytes, and antigen-presenting cells. The dialysis procedure itself can exacerbate oxidative stress by removing circulating antioxidants and stimulating leukocytes to produce reactive oxygen species. As a result, patients with ESRD develop a persistent imbalance between antioxidant defenses and prooxidant activity, ultimately promoting endothelial dysfunction, chronic inflammation, and progression of cardiac fibrosis [92].

Antioxidant therapy has been proposed as a potential strategy to improve cardiovascular outcomes in dialysis patients. Clinical studies suggest that N-acetylcysteine, a low-molecular-weight thiol with potent antioxidant properties, as well as β -carotene and vitamins A, C, and E, may reduce the risk of cardiovascular events in patients undergoing hemodialysis [92].

Electrolyte disturbances

The kidneys play a key role in maintaining homeostasis by continuously regulating the excretion and reabsorption of electrolytes and metabolic products. In CKD, impaired renal filtration, and in ESRD, the limited efficiency of dialysis, result in significant instability of electrolyte balance. Both hyperkalemia and hypokalemia have been independently linked to an increased risk of all-cause and cardiovascular mortality in patients with kidney failure [93].

Hyperkalemia is particularly common among ESRD patients receiving hemodialysis. It produces characteristic ECG changes, such as T-wave inversion, P-wave flattening, and widening of the QRS complex. Clinically, it can manifest as bradyarrhythmias, conduction disturbances, ventricular arrhythmias, and even asystole. Hyperkalemia may also drive a self-perpetuating cycle known as BRASH syndrome, which comprises bradycardia, renal failure, atrioventricular block, shock, and hyperkalemia. In this syndrome, both bradycardia and hyperkalemia may be drug-induced, particularly in elderly patients treated with β -blockers or calcium channel blockers for arrhythmias such as atrial fibrillation [94].

Hypokalemia occurs more frequently in patients with ESRD on peritoneal dialysis (PD). Ribeiro et al. demonstrated that serum potassium levels below 3.5–4 mmol/L were associated with an increased risk of all-cause and cardiovascular mortality, as well as with deaths from infectious diseases unrelated to PD [95].

Among the electrolyte disturbances characteristic of dialysis patients, hypomagnesemia is particularly important in the pathogenesis of vascular calcification. Reduced intracellular magnesium levels have been shown to promote proinflammatory and proatherogenic vascular injury by enhancing the production of reactive oxygen species, stimulating cytokine release, and activating endothelial cells. Magnesium supplementation has been shown to attenuate vascular calcification by disrupting calcium-phosphate crystal deposition within the vascular wall and by inhibiting the osteogenic transformation of vascular smooth muscle cells [96].

Immunosuppressive therapy

Standard immunosuppressive regimens for prevention of graft rejection typically combine calcineurin inhibitors (tacrolimus or cyclosporine) with either purine metabolism inhibitors (mycophenolate mofetil or azathioprine) or inhibitors of proliferative signal transduction (everolimus or sirolimus), often in conjunction with glucocorticosteroids (GCS) [97].

However, the adverse effects of these immunosuppressive drugs contribute to the development of CVD (Table 3). For example, post-transplant diabetes may occur with calcineurin inhibitors (CNIs), GCS, and proliferative response inhibitors, while anemia is often associated with mycophenolate mofetil and azathioprine [98]. CNIs can induce vascular remodeling and left ventricular hypertrophy, whereas proliferative response inhibitors and purine metabolism inhibitors have shown vasculoprotective and cardioprotective effects in certain studies.

Dyslipidemia is commonly linked to GCS, calcineurin inhibitors, and proliferative response inhibitors, but not to purine metabolism inhibitors. Arterial hypertension is promoted by CNIs and GCS, while some evidence suggests that proliferative response inhibitors and purine metabolism inhibitors may exert vasodilatory effects [99].

Kidney transplant dysfunction

Kidney transplant dysfunction is an important independent risk factor for CVD, primarily due to progression of hypertension, anemia, dyslipidemia, and hyperhomocysteinemia. According to published data, one year after KT, stage 3 CKD (estimated glomerular filtration rate, eGFR <60 mL/min/1.73 m²) is observed in about 60% of recipients, while stage 4 CKD (eGFR <30 mL/min/1.73 m²) develops in approximately 15% [100].

“Renal” risk factors for CVD become more pronounced as transplant function declines, particularly when eGFR falls below 60 mL/min/1.73 m² and even more so below 45 mL/min/1.73 m². Findings from the FAVORIT study demonstrated that CVD and all-cause mortality risks are significantly associated with eGFR <45 mL/min/1.73 m². In this group, each 5 mL/min/1.73 m² increase in eGFR corresponded to a 15% reduction in the risk of cardiovascular morbidity and mortality [101].

Proteinuria exceeding 1 g/day is observed in 20% of patients after KT [102]. In a study by Fernandez-Fresnedo et al., persistent proteinuria was shown to double the risk of CVD and overall mortality in KT recipients [103].

Although renin-angiotensin-aldosterone system (RAAS) blockers are widely used in patients with CKD and proteinuria, the evidence supporting their effectiveness in KT recipients remains inconclusive. A systematic review of 21 studies involving 1,549 patients demonstrated that RAAS blockade effectively reduced proteinuria after transplantation; however, the relatively short follow-up period (median 27 months) limited the ability to assess long-term outcomes for both graft and patient survival [104]. A subsequent systematic review of the same population found no significant effect of RAAS blockers on overall survival in KT recipients [105]. Similarly, a large retrospective study of 39,251 KT recipients showed that RAAS blockers did not reduce the risk of cardiovascular death compared with other classes of antihypertensive drugs [106]. Nevertheless, current clinical guidelines continue to recommend RAAS blockers for the management of proteinuria in KT recipients, given their demonstrated ability to reduce renal protein excretion [107].

Table 3

Side effects of immunosuppressive therapy [99]

Drug class	Hypertension	Dyslipidemia	Vascular remodeling, left ventricular hypertrophy	Diabetes	Anemia
Calcineurin inhibitors	+	+	+	+	
Proliferation signal inhibitors	–	+	–	+	
Purine metabolism inhibitors	–		–		+
Glucocorticosteroids (GCS)	+	+		+	

CONCLUSION

This review underscores the multifactorial nature of cardiovascular complications in patients with ESRD. Both renal pathology-related risk factors and the adverse effects of immunosuppressive therapy after KT play roles comparable in importance to traditional CVD risk factors. Early detection and targeted management of these factors are essential to reducing the burden of CVD in this patient population.

The authors declare no conflict of interest.

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