Cardiorenal Syndrome in End-Stage Kidney Disease

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Abstract
Background: Cardiorenal syndrome (CRS) in patients with end-stage kidney disease (ESKD) represents mainly cardiovascular disease (CVD) due to various complications associated with renal dysfunction—defined as type 4 CRS by Ronco et al.—because the effect of cardiac dysfunction on the kidneys does not need to be taken into consideration, unlike in non-dialysis dependent chronic kidney disease (CKD).

Summary: Patients with ESKD are often in a state of chronic inflammation due to the upregulation of proinflammatory cytokines. Chronic inflammation leads to malnutrition and consequently to vascular endothelial dysfunction and vascular calcification, which is referred to as malnutrition-inflammation-atherosclerosis (MIA) syndrome and acts as a major risk factor for CVD. Anemia also plays a crucial role in CVD, and individuals with erythropoietin-resistant anemia have a particularly high risk of CVD. However, caution is emphasized because not only anemia itself, but also the overtreatment of anemia with erythropoiesis-stimulating agents aimed at elevating hemoglobin to ≥ 13 g/dl can also increase the risk of CVD. In CKD-mineral and bone disorder (CKD-MBD), phosphate load triggers the interactions between various factors such as calcium, parathyroid hormone, vitamin D, and fibroblast growth factor 23, promoting vascular calcification and thus becoming a risk factor for CVD. Key Messages: In addition to traditional atherosclerosis risk factors such as hypertension, diabetes, and dyslipidemia, the involvement of MIA syndrome, anemia, and CKD-MBD accompanying CKD have also become a focus for investigation as major players in CRS in patients with ESKD.

Introduction

Chronic kidney disease (CKD) is often accompanied by cardiovascular disease (CVD) and together they contribute to a high mortality rate [1]. By the same token, patients with CVD have a high risk of renal dysfunction, and this bidirectional relationship is known as cardiorenal syndrome (CRS). Ronco et al. [2] proposed classifying CRS into five types according to the etiologic and chronologic interactions. For patients with end-stage kidney disease (ESKD), it is not necessary to take into account the effect of cardiac dysfunction on the kidneys because renal function is already abolished in these patients. Thus, CRS in these patients is essentially categorized as type 4 CRS because their cardiovascular system is affected by a wide range of clinical

Key Words
Anemia · Chronic kidney disease-mineral and bone disorder · Fibroblast growth factor 23 · Klotho · Malnutrition · Inflammation
manifestations, including uremia and anemia due to renal failure, abnormal calcium–inorganic phosphate metabolism, and vascular calcification [3] (fig. 1).

In this article, we review CRS in patients with ESKD, focusing on the effect of inflammation/malnutrition, anemia, and mineral and bone disorder (MBD) on the cardiovascular system.

### Risk Factors for CVD in CKD

To define the clinical manifestation of CVD in patients with CKD, Silverberg et al. [4] proposed the term ‘cardio-renal anemia syndrome’ (CRA syndrome) to conceptualize the association between anemia and cardiorenal failure, while Stenvinkel et al. [5] proposed the concept of malnutrition-inflammation-atherosclerosis (MIA) syndrome to define the close relationship between malnutrition/inflammation and arteriosclerosis. Moreover, patients with CKD also have a characteristic condition known as CKD-related mineral and bone disorder (CKD-MBD). In these patients, abnormal metabolism of minerals such as calcium and phosphate is involved in vascular calcification, which in turn greatly contributes to arteriosclerosis and CVD [6]. Therefore, CRA syndrome, MIA syndrome, and CKD-MBD are closely related to each other and together make up the pathological conditions of CRS seen in patients with CKD [7] (fig. 2).

![Fig. 1. Schematic illustration of type 4 chronic renocardiac syndrome. From Clementi et al. [3]. RAAS = Renin-angiotensin-aldosterone system.](image-url)
Inflammation and Malnutrition

Inflammation

In patients with CKD, inflammation is induced because of the enhanced production of proinflammatory cytokines by uremic toxin and impaired clearance due to renal dysfunction. According to Barreto et al. [8], the level of interleukin-6 increases with the progression of CKD stages and serves as a predictor of CVD and all-cause mortality. Similarly, the level of proinflammatory cytokines is a predictor of not only disease severity, but also death in patients with heart failure [9]. The mechanism underlying the induction of inflammation involves the activation of neurohumoral factors in the conventional pathway common to both heart and kidney failure as well as intestinal endotoxin absorption due to intestinal edema caused by venous congestion [9].

Malnutrition

In general, patients with CKD are often in a state of malnutrition referred to as protein energy wasting (PEW), in which body protein mass (skeletal muscles) and energy source (body fat) are reduced because of the involvement of multiple factors (e.g., the accumulation of toxins in the urine, inflammation, oxidative stress, and insulin resistance) in addition to a reduced oral intake [10]. PEW is observed in 30% of patients undergoing dialysis and is assessed based on serum albumin level and body mass index, both of which are risk factors for CVD [11, 12]. In 2005, Bouillanne et al. [13] developed the Geriatric Nutritional Risk Index as a simple tool to screen the nutrition state of elderly patients in daily clinical practice. In 2008, Yamada et al. [14] applied this index for patients undergoing dialysis and reported that patients with a low Geriatric Nutritional Risk Index score had poor prognosis and a significantly high risk of CVD.

MIA Syndrome

Malnutrition/inflammation and arteriosclerosis are closely related and mutually influence each other to generate a vicious cycle known as MIA syndrome [5]. The mechanism involves the promotion of proinflammatory cytokine synthesis and the activation of protein catabolism due to chronic inflammation, which inhibits albumin production in the liver and reduces muscle mass, thereby inducing malnutrition. Proinflammatory cytokines also suppress appetite, augmenting malnutrition. In addition, chronic inflammation damages the vascular endothelium through proinflammatory cytokines, causing cardiovascular and cerebrovascular complications.

Management of PEW and MIA Syndrome

To address these problems, it is important to perform adequate dialysis using pure dialysis fluids and biocompatible dialysis membranes, to manage hypertension and dyslipidemia, and to make lifestyle modifications by abstaining from tobacco and taking measures to prevent obesity, such as engaging in regular moderate exercise. A recent study also pointed out the importance of oral care, as periodontal disease can lead to chronic systemic inflammation [15].

Anemia

Involvement of Anemia in CRS

Anemia is prevalent in patients with CKD and those with heart failure. Anemia with a hemoglobin level of ≤12 g/dl is observed in 53.6% of CKD patients with an estimated glomerular filtration rate of 15–30 ml/min/1.73 m² and in approximately half of patients with heart failure [16, 17]. Unlike renal anemia due to erythropoietin deficiency, anemia in patients with heart failure causes an elevation in blood erythropoietin levels, suggesting

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Fig. 2. Schematic diagram of interactions among chronic kidney disease-related factors. MIA syndrome, CRA syndrome, and CKD-MBD interact with each other. Inflammation plays a central role in all three mechanisms. From Tsuruya and Eriguchi [7]. Ca = Calcium; P = phosphorus.
the presence of erythropoietin-resistant anemia due to inflammation. Thus, in CRS, anemia is mainly caused by erythropoietin deficiency and inflammation-induced erythropoietin resistance. Anemia should be treated appropriately because of its involvement in the mortality, duration of hospital stay, and readmission of patients with heart failure, as well as the prognosis of renal function in non-dialysis dependent CKD patients. Some controversy remains, however, over the effects of erythropoiesis-stimulating agents (ESA) and iron therapy on clinical outcomes such as quality of life and cardiac and renal prognosis [4, 18–21].

**Cause of Anemia in Patients with CKD**

Erythropoietin, a 30.4-kilodalton glycoprotein synthesized in the kidneys, stimulates the differentiation of erythroid stem cells and progenitors into red blood cells. The primary cause of anemia in patients with CKD is renal anemia induced by relative erythropoietin deficiency, in which the production of erythropoietin is insufficient to manage the reduction of hemoglobin. However, other factors are thought to be involved, including hematopoietic suppression due to uremia, reduced erythrocyte life-span, and impaired iron metabolism.

Anemia accompanying chronic infection, chronic inflammatory disease such as connective tissue disease, or malignant tumor is referred to as anemia of chronic disease (ACD), and the mechanism is thought to involve disorder of iron utilization caused by proinflammatory cytokines [22]. Specifically, proinflammatory cytokines upregulate the production of hepcidin in the liver and inhibit the intestinal absorption of irons and the transport of irons from the reticuloendothelial system to the bone marrow, leading to iron utilization disorder. In recent years, erythroferrone was identified as a molecule that suppresses the production of hepcidin in the liver and is thus associated with the clinical manifestation of ACD [23, 24]. In patients undergoing hemodialysis, ACD may be triggered by the production of proinflammatory cytokines caused by impure dialysis fluids or foreign substances such as a dialysis membrane and blood circuit.

**Important Considerations for Anemia Treatment**

The management of anemia in patients with CKD has been dramatically improved since the development of recombinant human erythropoietin, through the isolation and purification of erythropoietin from the urine of patients with aplastic anemia by Miyake et al. [25], and its clinical application in 1990. The subsequent production of long-acting ESA simplified the manipulation of hemoglobin levels. However, large-scale randomized controlled trials (RCTs) of anemia treatment conducted in recent years [21, 26, 27] showed that treatment of anemia with ESA aimed at elevating hemoglobin to ≥13 g/dl had not reduced CVD and all-cause mortality, but rather increased adverse events such as stroke.

**Prognosis of Patients with Hyporesponsiveness to ESA**

Secondary analyses of the RCTs suggested that adverse events developed frequently when a high dose of ESA was administered to achieve high levels of hemoglobin in patients who were hyporesponsive to the agent [28, 29]. In our cohort study (Q Cohort Study) of hemodialysis patients, those with hyporesponsiveness to ESA also had a reduced survival rate and a significantly high incidence of CVD [30]. These findings suggest the importance of establishing measures against ESA resistance.

**Measures against ESA Hyporesponsiveness**

Vitamin D improves ESA hyporesponsiveness and anemia [31] by suppressing the production of proinflammatory cytokines and directly inhibiting the expression of hepcidin at the transcriptional level [32]. Pentoxifylline was also reported to improve ESA hyporesponsiveness through its anti-inflammatory properties [33], and another RCT investigating the validity of pentoxifylline reported a tendency for the ‘ESA resistance index’ to decrease and hemoglobin levels to significantly increase [34]. However, the efficacy of hemodiafiltration in improving ESA responsiveness has been controversial. This is because the validity of hemodiafiltration has been shown in studies using non-ultrapure dialysis fluids in the control group, whereas most studies that reported its lack of validity had used ultrapure dialysis fluids in the control group, thus negating the validity of hemodiafiltration in the experimental group [35].

**CKD-MBD**

CKD-MBD is a generic term for bone mineralization disorders that accompany CKD and it includes laboratory abnormalities such as hyperphosphatemia, bone abnormalities, and vascular calcification. Because these abnormalities affect CVD and thus the prognosis of patients, CKD-MBD is regarded as an important risk factor for CVD [6].

CKD-MBD is induced by phosphate excretion impairment caused by a reduction in glomerular filtration rate.
The accumulation of phosphate triggers a series of reactions, such as the secretion of fibroblast growth factor 23 (FGF23) by osteoblasts, reduction in blood calcitriol levels, and secondary hyperparathyroidism, which is characterized by parathyroid hyperplasia and an increase in parathyroid hormone (PTH) [36]. Although these reactions begin in the early phase of CKD as compensatory mechanisms to prevent the accumulation of phosphate, they in turn start functioning as enhancers of CVD as renal function deteriorates further and the compensatory system fails.

**Abnormal Calcium–Phosphate Metabolism**

Through the elevation of FGF23 and PTH levels, phosphate not only increases the risk of mortality from CVD, but also itself becomes directly cytotoxic to the cardiovascular system. Under normal circumstances, phosphate is taken into cells by sodium-phosphate co-transporter 1 and used as a cellular component. However, when extracellular phosphate concentrations are high, intracellular phosphate activates the production of reactive oxygen species in the mitochondria, impairs endothelium-dependent vasodilatation, and induces the transformation of vascular smooth muscle cells into osteoblast-like cells, leading to vascular calcification [37, 38]. Using adenine-induced CKD rats, we have shown that inflammation, malnutrition, and oxidative stress play important roles in vascular calcification induced by phosphate load. We have also reported the improvement of vascular calcification by the application of antioxidants, thus revealing the association between CKD-MBD and MIA syndrome [39, 40].

A recent study also reported that inflammation and vascular calcification are induced directly by 30–150 nanometer calciprotein particles, that is, nanoparticle crystals of calcium and phosphate generated due to excess phosphate [41], suggesting the cytotoxic role of phosphate. Patients with CKD normally have hypocalcemia due to skeletal resistance to the action of PTH, lack of calcitriol, and hyperphosphatemia. However, they also sometimes develop hypercalcemia, so the opportunity to use calcium-containing phosphate binders and vitamin D receptor (VDR) agonists is increasing. Hypercalcemia and calcium loads are known to activate the intracellular signal transduction pathway involved in the calcification of vascular smooth muscle cells.

**Abnormal PTH–Vitamin D Metabolism**

In CKD, the parathyroid gland is activated as a compensatory mechanism against the accumulation of phosphate. While an elevation in PTH promotes the urinary excretion of phosphate, it also induces osteitis fibrosa, anemia, and cardiomegaly in the long run [42]. Because the active form of calcitriol is synthesized in the kidneys, calcitriol levels decrease with the progression of CKD. While a reduction in calcitriol causes secondary hyperparathyroidism, calcitriol also increases the risk of vascular calcification regardless of whether it is in excess or deficient [43]. Because calcitriol directly suppresses the expression of renin, the lack of calcitriol activates the renin-angiotensin-aldosterone system and thus increases the risk of CVD. It has been reported that VDR knockout mice develop hypertension associated with high renin levels and left ventricular hypertrophy (LVH) along with an increased formation of blood clots [44].

In CKD, the serum concentration of 25-hydroxyvitamin D, the precursor of calcitriol, is also low. The deficiency of 25-hydroxyvitamin D induces secondary hyperparathyroidism, a reduction in bone mass, and even a reduction of calcitriol, increasing the risk of mortality from CVD even in patients undergoing dialysis [45]. However, no improvement in LVH was found in the Prediction of Muscular Risk in Observational Conditions (PRIMO) Study, a recent randomized controlled study conducted to investigate the cardioprotective effect of paricalcitol [46].

**FGF23 and Klotho**

FGF23 is secreted from osteocytes in response to phosphate loads to promote the urinary excretion of phosphate by downregulating the expression of type IIc sodium-phosphate cotransporter in the proximal tubules and to suppress the intestinal absorption of phosphate by inhibiting the production of calcitriol in the kidneys, thus shifting the phosphate balance in a negative direction. To activate FGF receptor, FGF23 requires Klotho, which is synthesized mainly in the kidneys. Because the level of Klotho decreases as renal function deteriorates, the urinary excretion of phosphate decreases in patients with CKD because of FGF23 dysfunction. The subsequent accumulation of phosphate stimulates the production of FGF23, initiating the elevation of blood FGF23 levels in the early phase of CKD. Phosphate accumulation due to the dysfunction of FGF23 promotes vascular calcification. A recent study has shown the association between FGF23 and LVH, CVD, or survival in patients with CKD as well as in healthy individuals [47], prompting a debate on whether FGF23 is a mere ‘biomarker’ or a ‘toxin’. While some studies have reported the direct enlargement of cardiomyocytes by FGF23 in the absence of Klotho [48] and indirect induction of volume expansion, hypertension, and cardiac hypertrophy through the activation of sodium reabsorption in the renal tubule by FGF23 [49],
other studies have reported contradictory findings [50, 51], necessitating further research into these issues.

The anti-aging protein Klotho is synthesized mainly in the kidneys and its level begins to decline in the early phase of CKD. Klotho functions as an obligatory co-receptor that is needed for FGF23 to specifically bind to the FGFR receptor. A reduction in Klotho level promotes vascular calcification through FGF23 dysfunction, reduction of urinary phosphate excretion, and accumulation of phosphate. Furthermore, Klotho has been reported to directly inhibit vascular calcification, protect endothelial cells, and suppress cardiomegaly without the involvement of FGF23, suggesting that Klotho deficiency is a risk factor for CVD [52, 53].

Summary
Cardiorenal syndrome in patients undergoing dialysis is characterized by type 4 CRS manifestations. In addition to the traditional risk factors for arteriosclerosis such as hypertension, diabetes, and dyslipidemia, mutual interactions between inflammation/malnutrition, anemia, and CKD-MBD contribute to the high risk of CVD (fig. 2).

Conflicts of Interest
All authors declare that they have no conflicts of interest.

References


