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Review

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Phosphate and Coronary Artery Disease in Patients with Chronic Kidney Disease

Hiroaki Ogata[1, 2], Hirohito Sugawara[1], Masahiro Yamamoto[1] and Hidetoshi Ito[1]

[1]Division of Nephrology, Department of Internal Medicine, Showa University Northern Yokohama Hospital, Yokohama, Japan
[2]Department of Medical Education, Showa University School of Medicine, Tokyo, Japan

Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD). Both traditional and CKD-related factors are associated with CVD in CKD patients. Traditional factors that play an important role in the atherosclerotic process directly contribute to a higher risk of coronary artery disease in patients with early-stage CKD. Among CKD-related factors, CKD–mineral and bone disorder plays a critical role in the pathomechanism of nonatherosclerotic diseases, which increases the risk of cardiovascular morbidity and mortality in patients with advanced CKD. Higher serum phosphate levels were significantly associated with cardiovascular events and all-cause mortality in patients with or without CKD. An increased phosphate load, directly and indirectly, promotes arterial medial calcification and left ventricular hypertrophy, both of which predispose patients to coronary artery disease. Calciprotein particles that form in a hyperphosphatemic state promote the transformation of vascular smooth muscle cells (VSMCs) into osteoblastic cells, thereby providing a scaffold for medial calcification in the artery. Increases in fibroblast growth factor-23 and disturbed vitamin D metabolism induced by an excessive phosphate load play a significant role in the development of cardiomyocyte hypertrophy and cardiac fibrosis. Recently, hyperphosphatemia was reported to promote *de novo* cholesterol synthesis in VSMCs and macrophages, which is likely to contribute to statin resistance in patients with end-stage kidney disease. This review outlines the association between increased phosphate load and coronary artery disease in patients with CKD.

Key words: **CKD, Phosphate, CKD–MBD, Coronary artery disease, Cardiovascular disease**

I. Introduction

The kidneys play a central role in mineral and bone metabolism. Many studies have found that altered mineral and bone metabolism in patients with chronic kidney disease (CKD) is associated with a high risk of cardiovascular disease (CVD) and all-cause mortality[1-3]. Thus, a new concept, "CKD–Mineral and Bone Disorder (CKD-MBD)," which includes abnormal biomarkers (calcium, phosphate, parathyroid hormone (PTH), and vitamin D), bone disease, and vascular calcification, was proposed in the 2000s[1]. Although this concept is currently widely accepted and understood, there are still many unresolved issues. In addition to mineral and bone metabolism, phosphate is an essential mineral that plays an important role in many metabolic processes in the human body, including energy production, DNA and RNA synthesis, and intracellular signal transduction[4, 5]. Phosphate homeostasis is maintained by a complex and elaborate interorgan network in the body[4, 5]. The kidneys play a pivotal role in this network, as excess phosphate is mainly excreted in the urine **(Fig. 1)**. Therefore, phosphate homeostasis is inevitably disturbed as glomerular filtration rate (GFR) declines. In the early stages of CKD, serum phosphate levels are not elevated due to multiple compensatory mechanisms, including increases in PTH and fibroblast growth factor 23 (FGF-23), both of which have phosphaturic action[4, 5]. However, hyperphosphatemia easily develops after CKD stage 4 [4-6]. In compensatory mechanisms against increased

Address for correspondence: Hiroaki Ogata, Division of Nephrology, Department of Internal Medicine, Showa University Northern Yokohama Hospital, Yokohama, Japan E-mail: ogatah@med.showa-u.ac.jp

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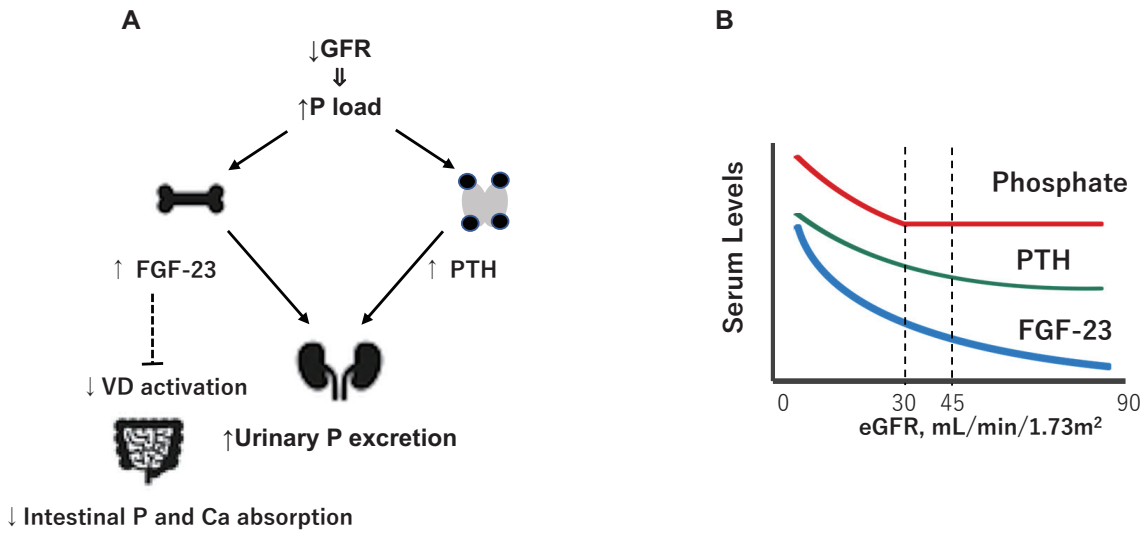

Fig. 1. Compensatory mechanism for increased phosphate load.

P load to the body increases as GFR declines (urinary P excretion decreases). Increased P load induces synthesis and secretion of both FGF-23 in bone tissue and PTH in the parathyroid gland. FGF-23 and PTH increase urinary P excretion. Furthermore, FGF-23 suppresses vitamin D activation and then decreases intestinal P absorption (A). Serum P levels are not observed in most patients with mild to moderate CKD due to the above compensatory mechanisms. Consequently, serum levels of FGF-23 and PTH rapidly rise at the cost of increased P load as CKD progresses (B). P, phosphate; GFR, glomerular filtration rate; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone; CKD, chronic kidney disease

phosphate load, excessive PTH secretion impairs bone metabolism, resulting in various bone lesions. In addition, FGF-23 inhibits not only phosphate reabsorption (increase in urinary phosphate excretion) but also vitamin D activation, causing activated vitamin D deficiency. Despite markedly increased serum PTH and FGF-23 levels in end-stage kidney disease (ESKD), compensatory mechanisms eventually fail, and hyperphosphatemia develops. The main problem with hyperphosphatemia is that it is directly or indirectly associated with clinical outcomes in patients with CKD[7-21]. This article focuses on the association between hyperphosphatemia and CVD, particularly coronary artery disease, in patients with CKD, describing the facts that have been revealed and the challenges that lie ahead.

II. Cardiovascular Disease in CKD

CVD remains as the leading cause of death in patients with CKD[22-26]. CVD comprises of both atherosclerotic and nonatherosclerotic diseases. Indeed, the same individual often has both the traits. However, the impact of CKD progression appears to be different[26, 27]. In an analysis of the CKD-JAC study, a large-scale prospective cohort study in Japan, the incidence of CVD was reported to increase from 11.9 to 39.4 per 1000 person-years across CKD stages 3b–5 [28]. In addition, this study demonstrated that the incidence of atherosclerotic disease, including coronary artery disease and stroke, was similar across CKD stages 3a–5; however, the incidence of congestive heart failure significantly increased as CKD stage advanced[28]. The impact of CKD and its progression on atherosclerotic diseases, including coronary artery disease and ischemic stroke, is likely to be smaller than that on nonatherosclerotic diseases, such as heart failure, sudden death, and arrhythmia[2, 26, 29, 30, 31]. The increase in nonatherosclerotic disease is greater than that in atherosclerotic disease in patients with advanced CKD[1, 26, 30, 31]. Although CVD becomes more prevalent as CKD progresses, the atherosclerotic disease to CVD ratio declines. Cheung found that CVD was associated with neither serum levels of total cholesterol nor systolic blood pressure in patients undergoing hemodialysis[32]. The high morbidity and mortality of CVD in patients with CKD are attributed to both traditional and CKD-related factors **(Table 1)**[26, 31, 33-36]. In addition to traditional factors, CKD-related factors, including chronic volume excess, anemia, uremic toxins, and CKD-MBD, contribute to arterial medial calcification and left ventricular hypertrophy (LVH), both of which are risk factors for coronary artery disease[1, 26, 31, 33-37].

Coronary artery disease is more prevalent in patients with CKD than in those without CKD[25, 38, 39]. Previous studies have reported that both traditional and CKD-related factors accelerate the atherogenic process

Table 1. Traditional and CKD-specific factors for cardiovascular disease risk

Traditional factors	CKD-related factors
• Advanced age • Male • Diabetes • Hypertension • Dyslipidemia • Smoking	• Lower GFR • Albuminuria • Uremic toxin • Volume overload • CKD-MBD ◇Hyperphosphatemia ◇Hypercalcemia ◇Abnormal vitamin D metabolism ◇High FGF-23

CKD, chronic kidney disease; GFR, glomerular filtration rate; CKD-MBD, CKD-Mineral and Bone Disorder; FGF-23, fibroblast growth factor-23

and result in coronary artery disease in CKD[13, 40, 41]. It is easily assumed that as CKD progresses, the influence of CKD-related factors becomes stronger than that of traditional factors. CKD-related factors also contribute to arterial medial calcification and LVH, which play critical roles in the pathophysiology of nonatherosclerotic disease[26, 31, 34, 37]. Consequently, nonatherosclerotic events are more prevalent than coronary artery disease in patients with advanced CKD[26, 42-46]. Heart failure, sudden death, and arrhythmia are more common causes of death than coronary artery disease in patients with ESKD[26, 42-46].

An analysis of 126 autopsy cases in the Hisayama study revealed that advanced atherosclerotic lesions increased as the eGFR declined[47]. Interestingly, neither hypertension nor dyslipidemia was associated with the presence of advanced coronary atherosclerotic lesions, whereas diabetes was significantly associated with it[47]. A study of a cohort of patients with early-stage CKD in Korea demonstrated that CKD was associated with a higher prevalence of coronary atherosclerosis, which was identified via computed tomography (CT) angiography[48]. In a community-based cohort study in Canada, although there was no significant association between coronary atherosclerosis and eGFR, albuminuria was an independent risk factor for coronary atherosclerosis in patients with a given GFR[49]. A cross-sectional study from a single center in Japan reported that the prevalence of right coronary artery lesions significantly increased as CKD progressed[50]. A study in the early 2000s found that coronary angiography showed coronary artery stenosis in 53% of asymptomatic patients who were newly started on dialysis[51]. Iwasaki *et al.* reported that the prevalence of coronary artery disease in patients newly started on hemodialysis significantly decreased from 69% to 25% between 1993 and 2010 in a single medical center[52]. Serum high-density lipoprotein (HDL) cholesterol levels significantly increased during the observational period, whereas serum C-reactive protein levels significantly decreased. In parallel, the use of erythropoietin and renin–angiotensin system inhibitors significantly increased during this period[52]. Contemporary medical management of CKD and CVD is likely to reduce the prevalence of coronary artery, even in patients with ESKD[52]. Previous observational studies demonstrated that not only was the risk and mortality rate of coronary artery disease significantly higher in patients with CKD than in the general population or those without CKD[53-57], but also the incidence of acute myocardial infarction and the cardiovascular mortality rate were significantly higher in patients with eGFR between 15 and 59 mL/min/1.73 m^2 than in those with eGFR ≥ 60 mL/min/1.73 m^2 [56]. A *post hoc* analysis of the VALIANT trial revealed that even a mild GFR reduction was significantly associated with a higher risk of cardiovascular complications after acute myocardial infarction[55]. The results of a cohort study conducted from 1988 to 1997 in Okinawa, Japan, indicated that the incidence of acute myocardial infarction was much higher in patients undergoing hemodialysis (4.1 times in men; 6.1 times in women) than in the general population[53]. Notably, the mortality rate within 1 month after acute myocardial infarction was as high as 49.2% in patients undergoing hemodialysis compared with 22.9% in the general population[53]. It has been suggested that the reason for the poor prognosis of patients with lower GFR after acute myocardial infarction is that they are not treated as well as those with normal kidney function[54]. In fact, it was reported that patients with low GFR were less likely to undergo coronary angiography and revascularization, which is an established therapy for acute myocardial infarction, than those with preserved kidney function,

probably because patients with low GFR are at a higher risk of acute kidney injury and overall death after percutaneous coronary intervention[58, 59].

Both traditional and CKD-related factors contribute to the pathophysiology of coronary artery disease in CKD, and the intensity of involvement of these two factors appears to change as CKD progresses. Recently, among the CKD-related factors, CKD-MBD, particularly hyperphosphatemia, has received particular attention as an etiological and modifiable factor for cardiovascular events in patients with CKD[1-3].

III. Phosphate on Clinical Outcomes

In the past few decades, many observational studies in the general population and in patients with CKD have reported that elevated serum phosphate concentrations, even within the normal range, are associated with an increased risk of CVD and all-cause mortality[9, 60]. Since then, the association between phosphate and cardiovascular events has attracted great attention, and experimental and clinical studies have been conducted to elucidate many novel mechanisms of excessive phosphate toxicity in various organs. Excessive phosphate load leads to endothelial dysfunction[61]. In addition, clinical and experimental studies have demonstrated that hyperphosphatemia promotes arterial medial calcification and LVH, both of which predispose individuals to coronary artery disease. Ishimura *et al.* found a positive association between serum phosphate concentrations and carotid intima-media thickness, an index of atherosclerosis, in patients undergoing hemodialysis[62]. Furthermore, it has been reported that higher serum phosphate concentrations, even within the normal range, are associated with a higher risk of coronary artery disease in patients with previous myocardial infarction[7]. T50, a measure of vascular calcification propensity, predicts acute myocardial infarction in patients undergoing hemodialysis[63]. However, it remains unknown whether excessive phosphate loading directly contributes to atherosclerosis. An experimental study has reported that microcalcification in the fibrous cap of an atheroma is associated with plaque instability[64, 65]. Higher serum phosphate concentrations might promote intimal calcification and, consequently, be associated with an increased risk of atheroma plaque rupture in patients at risk of coronary artery disease[34, 35]. Recently, among the CKD-related factors, CKD-MBD, particularly hyperphosphatemia, has received great attention as an etiological and modifiable factor for cardiovascular events in patients with CKD[1-3].

IV. Phosphate on Cardiac Remodeling Predisposing to Coronary Artery Disease

In patients with CKD, premature aging, including medial arterial calcification, LVH, and cardiac fibrosis, accelerates as the kidney function declines[26, 36, 37, 66]. Arterial medial calcification frequently develops in CKD, and excessive phosphate load is thought to play a critical role in its pathophysiology[37]. The incidence of LVH significantly increases as CKD progresses, and the presence of LVH is a strong predictor of CVD and all-cause mortality[26]. Many experimental and clinical studies have shown that an increased phosphate load promotes LVH through direct and indirect mechanisms[26, 37].

1. Arterial Medial Calcification

Arterial calcification can be mainly classified into intimal calcification, which is observed in atherosclerotic lesions, and medial calcification, both of which are frequently observed in individuals with advanced age, diabetes, and CKD[26, 30, 67-72]. Atherosclerosis and arterial medial calcification simultaneously develop as the CKD progresses[64, 67]. Traditional factors, including advanced age, diabetes, dyslipidemia, hypertension, and smoking, play major roles in the development of atherosclerosis, whereas CKD-related factors mainly contribute to arterial medial calcification **(Fig. 2)**. Arterial medial calcification is characterized by extended thickening and calcification of the medial layer of the arteries[36, 37, 67]. Unlike atherosclerotic lesions, arterial medial calcification does not directly cause narrowing or occlusion of the artery lumen. However, the increase in arterial stiffness associated with arterial medial calcification not only increases cardiac afterload but also decreases coronary blood flow, which mainly depends on diastolic blood pressure[26, 30, 31, 36, 37, 73, 74]. In addition, an increase in cardiac afterload promotes LVH, which increases the oxygen demand in myocardial tissues. Therefore, arterial stiffness can be a predisposing factor for myocardial ischemia[75-79].

Numerous experimental and clinical studies have demonstrated that CKD-MBD plays a critical role in the development and progression of arterial medial calcification. Although the precise pathomechanism of arterial medial calcification in CKD is not fully understood, an increased phosphate load as kidney function declines is likely to be a major driver of arterial medial calcification[31, 36, 37, 80]. Arterial medial calcification and calcified plaques within atherosclerotic lesions are frequently present in the same patient, making it difficult to distinguish

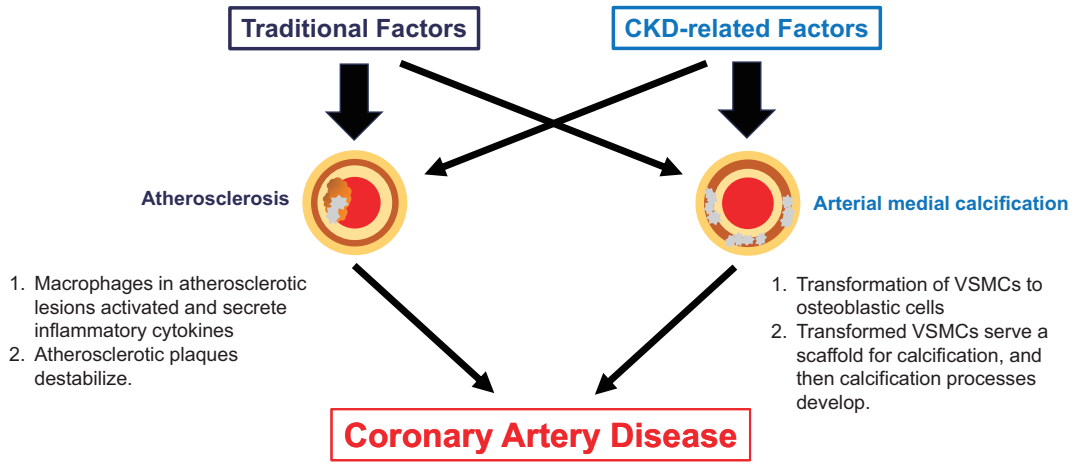

Fig. 2. Traditional and CKD-related factors for atherosclerosis and arterial medial calcification.

While traditional factors mainly contribute to the atherosclerotic process, CKD-related factors are likely to play an important role in the arterial medial calcification process, which includes calcification of VSMCs transforming to osteoblastic cells. Both traditional and CKD-related factors are involved in atherosclerotic and arteriosclerotic processes, and consequently, patients with CKD are predisposed to CAD. CKD, chronic kidney disease; VSMCs, vascular smooth muscle cells; CAD, coronary artery disease

between the two calcified lesions using current imaging techniques[27, 71, 81]. The presence of calcified lesions in atherosclerosis is more prevalent in patients with risk factors such as advanced age, diabetes, dyslipidemia, hypertension, CKD, and smoking[82, 83]. As CKD progresses, arterial medial calcification in the coronary artery becomes more prevalent. Patients undergoing dialysis often experience severe coronary artery calcification, and a longer dialysis duration is a significant predictor of advanced coronary artery calcification[69, 84-86]. The coronary artery calcification score, measured using CT, cannot differentiate between intimal calcification in atherosclerotic plaques and medial calcification. However, it is likely to be a significant predictor of cardiovascular events and all-cause mortality not only in patients without CKD but also in those with CKD[68, 85, 88]. It is noteworthy that the coronary artery calcification score is significantly associated with a higher risk of coronary artery disease in the general population and in patients undergoing dialysis[70, 72].

The mechanism of arterial medial calcification is considered to involve two pathological processes, namely, osteoblastic transformation of vascular smooth muscle cells (VSMCs) and calcium phosphate deposition **(Fig. 3)**[79, 80, 89-91]. Excess extracellular phosphate ions easily bind to extracellular calcium ions, leading to the formation of amorphous calcium phosphate. Subsequently, calcium phosphate precipitates combine with fetuin-A to form complexes known as calciprotein monomers[80, 92]. These monomers aggregate to form primary calciprotein particles (CPPs). In the next step, primary CPPs further aggregate to generate secondary CPPs, which undergo transformation from amorphous to crystalline calcium phosphate over time. Secondary CPPs have been found to exert toxic effects on various cells[79, 80, 89-91]. They induce the transformation of VSMCs into osteoblast-like cells via NFκB activation. Transformed VSMCs are more susceptible to calcification[93]. Transformed osteoblasts secrete a matrix that serves as a scaffold for calcification. In addition, macrophages are activated by secondary CPPs and secrete TNF-α, IL-1β, and IL-18 [80, 93]. Secondary CPPs have been suggested to induce apoptosis of VSMCs and macrophages, potentially resulting in atherosclerotic plaque instability and rupture[37, 80, 93]. Furthermore, CPP-associated proinflammatory and oxidative conditions may accelerate the atherosclerotic process, posing a higher risk of cardiovascular events[35, 37, 79, 80].

Magnesium is a natural inhibitor of calcification[94]. It has been reported to suppress arterial medial calcification by inhibiting the transformation of primary CPPs into secondary CPPs[95]. Sakaguchi *et al.* reported that magnesium oxide delayed the progression of coronary artery calcification in patients with CKD stages 3–4 [96]. A secondary analysis of a randomized controlled trial (RCT) revealed that high-dose administration of sucroferric oxyhydroxide, a potent phosphate binder, reduced endogenous CPP formation in patients with hyperphosphatemia undergoing hemodialysis[97]. In addition, the serum from sucroferric oxyhydroxide-treated patients exhibited lower inflammatory

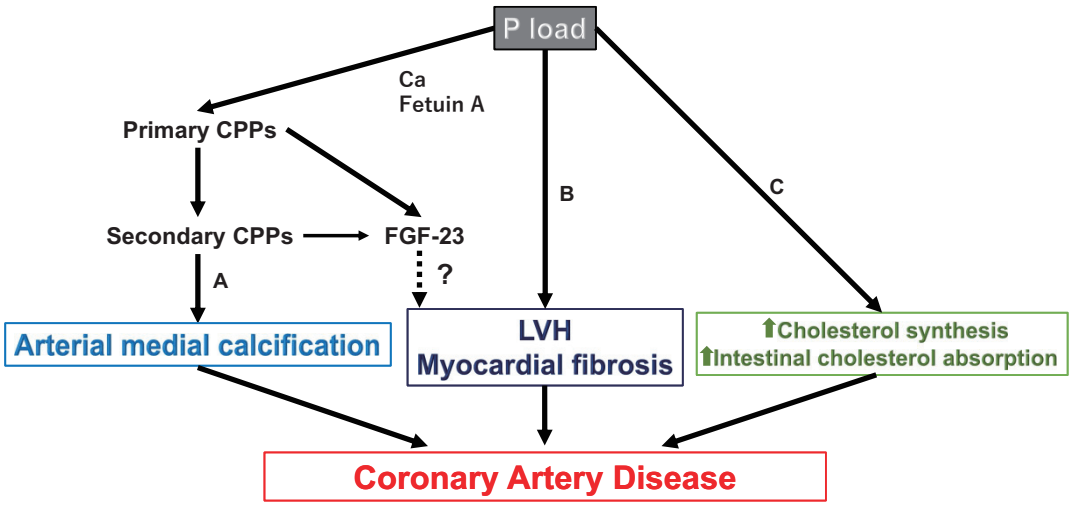

Fig. 3. Effect of P load on cardiovascular remodeling and local cholesterol metabolism.

Excessive calcium and phosphate ions in the blood form amorphous calcium phosphate, and then calcium phosphate precipitates bind to fetuin-A. These complexes aggregate to form primary CPPs. Subsequently, primary CPPs further aggregate to transform into secondary CPPs. Secondary CPPs have toxic actions that induce not only synthesis and secretion of FGF-23 but also arterial medial calcification. Increased P load and FGF-23 promote LVH and cardiac fibrosis, both of which predispose patients to coronary artery disease (A,B). Hyperphosphatemia is recently reported to increase *de novo* cholesterol synthesis in VSMCs cells and macrophages. This change might accelerate the atherosclerotic process (C).

P, phosphate; CPPs, calciprotein particles; FGF-23, fibroblast growth factor 23; VSMCs, vascular smooth muscle cells

properties[97]. Although hyperphosphatemia has been reported to be a significant predictor of cardiovascular events, the relationship between hyperphosphatemia and cardiovascular mortality in Japanese patients undergoing hemodialysis was significantly affected by serum magnesium concentration[98]. This relationship disappeared as the serum magnesium concentrations increased[98].

2. LVH

The prevalence of LVH, a reliable CVD predictor, increases with CKD progression, as well as arterial medial calcification[75, 76, 100, 101]. Experimental and clinical studies have demonstrated that the characteristic structural changes in the LVH of CKD include cardiomyocyte hypertrophy, myocardial microarteriopathy, and myocardial fibrosis[26, 75, 102, 103]. Myocardial fibrosis in CKD is characterized by collagen deposition between cardiomyocytes and arterioles[26, 102-104]. These changes, including cardiomyocyte hypertrophy and reduced capillary densities, result in a mismatch between cardiomyocytes and the capillary supply, despite the increased demand for oxygen and blood flow due to LVH[26, 36, 37, 102]. Furthermore, myocardial fibrosis surrounding the capillaries might impair oxygen and blood flow supply. Thus, patients with CKD who present with LVH are likely to be vulnerable to ischemia. An experimental study found that pathological changes can occur even in early-stage CKD[102-103].

The development of LVH in CKD is attributed to various factors, including hypertension, chronic volume overload, activated renin–angiotensin system, sympathetic overactivation, and CKD-MBD[36, 37, 66]. Within the context of CKD-MBD, hyperphosphatemia and disturbed vitamin D metabolism are likely to play significant roles in the mechanism of LVH in CKD (Fig. 3)[37, 105-108]. Previous studies have consistently demonstrated a significant association between hyperphosphatemia and LVH in patients with CKD and the general population[109-113]. Experimental studies have confirmed that excessive phosphate loads cause LVH with myocardial fibrosis[105-108]. The hypothesis that increased FGF-23 induced by phosphate load directly causes LVH has gained attention[114]. In its natural function, FGF-23 exerts urinary phosphate excretion by inhibiting phosphate resorption in the proximal tubule and decreases intestinal phosphate absorption through the suppression of vitamin D activation (Fig. 1)[115]. In addition, FGF-23 has been suggested to exert various off-target effects on multiple organs[114, 116]. Many observational studies have shown significant associations between serum FGF-23 levels and clinical outcomes, including cardiovascular events and all-

cause mortality[117-120]. Experimental studies have suggested that excessive FGF-23 promotes LVH and myocardial fibrosis[37, 66, 115, 121]. However, there are arguments against "the FGF-23 hypothesis." Despite the rapid increase in serum FGF-23 levels in patients with CKD as kidney function declines, the risk of CVD does not necessarily increase in proportion to the increase in serum FGF-23 levels[119]. This finding suggests that the hypothesis of the cardiovascular toxicity of FGF-23 is not supported. Furthermore, controversy continues regarding whether FGF-23 is a causative substance or biomarker reflecting the pathophysiology of myocardial injury, as it has been reported to be secreted from injured cardiomyocytes[122]. In hereditary hypophosphatemic rickets and animal models, serum FGF-23 levels are elevated, but LVH is not observed[123].

V. Effect of Phosphate on Statin Resistance

Dyslipidemia is a well-established risk factor for atherosclerosis and subsequently for coronary artery disease. In patients with CKD, atherogenic dyslipidemia, characterized by higher levels of triglycerides and LDL cholesterol, and lower levels of HDL cholesterol, is likely to be prevalent[124]. Interestingly, serum LDL cholesterol levels were less predictive of coronary artery disease in patients with CKD than in the general population[125]. Furthermore, the favorable effects of statins might be compromised in patients with ESKD[126]. Statin use significantly improves the risk of cardiovascular events and reduces all-cause mortality in patients with normal kidney function or CKD. However, the efficacy of statins in patients with ESKD remains unknown[127]. Two previous randomized clinical trials demonstrated that statins did not reduce CVD events in patients undergoing dialysis[128, 129]. Although the underlying mechanisms that impair the effects of statins in patients undergoing dialysis remain unknown, recent studies have suggested a possible mechanism by which hyperphosphatemia contributes to statin resistance. Zhou *et al.* reported that increased extracellular phosphate concentrations induced overexpression of sterol regulatory element-binding protein 2 (SREBP2), a master regulator of genes involved in cholesterol uptake and synthesis, including 3-hydroxy-3-methylglutaryl coenzyme A reductase[130]. Thus, hyperphosphatemia-induced SREBP2 overexpression might increase *de novo* cholesterol synthesis in VSMCs and macrophages and consequently promote the atherosclerotic process. Excessive phosphate load might accelerate the atherosclerotic process through increased cholesterol synthesis in VSMCs and macrophages despite statin treatment **(Fig. 3)**.

More recently, Shoji *et al.* found a significant positive association between serum phosphate concentration and serum campesterol concentration, a marker of intestinal cholesterol absorption, in patients undergoing hemodialysis treated with statins or ezetimibe for hypercholesterolemia[131]. Taken together, as a possible mechanism of the statin-resistant state in CKD, excessive phosphate load might induce not only increased intestinal cholesterol absorption but also increased local cholesterol synthesis. Notably, a secondary analysis of the AURORA trial revealed that higher levels of serum phosphate might impair the clinical benefit of statin treatment in patients undergoing dialysis[132].

VI. Conclusion

Arterial medial calcification and LVH, which are caused by excessive phosphate load, are predisposing factors for the development of coronary artery disease **(Fig. 3)**[26, 33-37]. Arterial medial calcification not only promotes LVH by increasing afterload but also leads to a decrease in coronary blood flow. In patients with CKD, there is an increased demand for blood supply and oxygen to myocardial tissues owing to LVH[26, 102]. Myocardial fibrosis can result in impaired blood supply and oxygen delivery[26, 33-37, 102, 103]. These pathological alterations in the cardiovascular system in CKD are likely to be vulnerable to cardiac ischemia. In addition, hyperphosphatemia is suggested to promote *de novo* cholesterol synthesis and increase intestinal cholesterol absorption[130, 131] and, consequently, directly accelerate the atherosclerotic process in patients with ESKD. This hypothesis is supported by the results of RCTs showing that statins did not reduce cardiovascular events or all-cause mortality in patients undergoing dialysis[128, 129].

The above outlines the relationship between phosphate and coronary artery disease in CKD. Many studies have suggested that excessive phosphate load is significantly associated with a higher risk of CVD, including coronary artery disease. Therefore, does treatment for hyperphosphatemia reduce the risk of cardiovascular events and all-cause death? An observational study suggested that the use of phosphate binder was significantly associated with a lower risk of cardiovascular and all-cause mortality in patients undergoing hemodialysis[133]. However, no clinical trial has provided definitive evidence that phosphate-lowering treatment could reduce the risk of coronary artery disease. Furthermore, there is a controversy over the choice of phosphate binders for patients with hyperphosphatemia. Currently, several

types of phosphate binders are clinically available in patients with both hyperphosphatemia and CKD. Among them, calcium-based phosphate binders, including calcium carbonate and calcium acetate, have been used in clinical setting for a long time owing to their tolerability and low cost. Observational studies demonstrated that hypercalcemia, as well as hyperphosphatemia, was also associated with higher risks of cardiovascular events and all-cause mortality in patients with ESKD through accelerated cardiovascular calcification induced by increased calcium load[2, 3]. The updated Kidney Disease: Improving Global Outcomes (KDIGO) guidelines published in 2017 recommend restricting the dose of calcium-based phosphate binders for hyperphosphatemia[2]. However, the Cochrane Database of Systematic Review in 2018 reported that it was inconclusive whether calcium-free phosphate binders reduced cardiovascular events compared with calcium-based phosphate binders based on the results from RCTs comparing calcium- and non-calcium-based phosphate binders[134]. A recent RCT, LANDMARK, which was larger in scale and had a longer follow-up period than previous ones, demonstrated that there was no significant difference in cardiovascular events, including ischemic heart disease, and all-cause mortality between calcium carbonate- and lanthanum carbonate-based treatments among patients undergoing hemodialysis with hyperphosphatemia and with at least one vascular calcification risk factor in Japan[135]. In addition, a subsidiary of the LANDMARK trial found that lanthanum carbonate-based treatment for hyperphosphatemia did not delay coronary artery calcification for 2 years compared with calcium-based treatment[136]. These results indicate that calcium-based phosphate binders do not necessarily contribute to vascular calcification and increase the risk of cardiovascular events and death compared with non-calcium-based phosphate binders. However, these results may not be applicable to all patients worldwide. This is because dietary calcium intake widely varies by region, and it is known that the dietary calcium intake of people in Asia and Africa is less than half that of Western countries. The results from the LANDMARK trial indicate that calcium-based phosphate binders, at least in patients with low dietary calcium burden, are well tolerated and safe, unless their doses are excessive[135].

The above is an overview of the relationship between increased phosphate load and coronary artery disease in CKD. In phosphate management, there are many issues to be addressed, including not only pharmacological intervention but also optimal target range of serum phosphate concentration. Further investigation is warranted to determine whether aggressive phosphate management is useful for the prevention of CVD, including coronary artery disease, in patients with CKD and hyperphosphatemia.

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Conflict of Interest

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