Regulatory effects of nutritional and metabolic disorders on vascular calcification in chronic kidney disease: a narrative review

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Background and Objective: Vascular calcification (VC) is common in chronic kidney disease (CKD) patients and is associated with poor cardiovascular outcomes. This study aims to review nutritive pro-calcifying factors of CKD.

Methods: Electronic databases (PubMed, EMBASE, Cochrane) were searched from 2001 as at July 26, 2022, to select and summarize the basic and clinical studies reporting the effects of malnutrition or metabolic disorders on VC in CKD and the evolving treatments for these nutrient metabolic disorders.

Key Content and Findings: Hyperphosphatemia, calcium load, hypomagnesemia, iron deficiency, lipoprotein(a) abnormalities, protein malnutrition, and vitamin K deficiency secondary to CKD were closely associated with the occurrence and development of VC. Elevated phosphate and calcium levels were essential contributors to VC, yet current phosphate binders with good phosphate-lowering effects had not been shown to delay VC progression in CKD, and it remained challenging on how to identify and prevent calcium overload. Magnesium supplementation was the most promising treatment for mitigating VC, as supported by *in vitro* and *in vivo* studies and clinical trials. Correction of iron and vitamin K deficiency might contribute to VC attenuation, yet there was a lack of clinical evidence on CKD patients.

Conclusions: This review highlighted the effects of nutrient metabolism disorders on CKD-VC, and additional studies are needed to further address optimal nutrition strategies for mitigating VC in CKD.

Keywords: Chronic kidney disease (CKD); vascular calcification (VC); mineral disorders; lipid abnormalities; protein malnutrition

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Introduction

Vascular calcification (VC) in chronic kidney disease (CKD) is a process of differentiation of vascular smooth muscle cells (VSMCs) from a contractile phenotype to an osteogenic/osteochondral phenotype (1). The prevalence of VC in nondialysis CKD patients and dialysis patients is 45–70% and 52–90%, respectively, which is 2–3 times higher than that in patients with normal renal function, and VC poses a high risk of cardiovascular disease (2-4). A prospective observational study involving 1,541 adult CKD patients

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Table 1 Summary of the search strategy

Items	Specification
Date of search	April 10, 2022 to July 26, 2022
Databases	PubMed, Embase, and the Cochrane Library
Search terms	MeSH: (("Vascular Calcification/diet therapy"[Mesh]) OR "Vascular Calcification/metabolism"[Mesh]) OR "Vascular Calcification/prevention and control"[Mesh]
	Free text: Chronic Kidney Disease; Vascular Calcification; Artery Calcification; Phosphate; Phosphate-Lowering Agents; Ferric Citrate; Sucroferric Oxyhydroxide; Calcium; Magnesium; Iron; Dyslipidemia; Low-Density Lipoprotein Cholesterol; Lipoprotein(a); Malnutrition; Vitamin K
	Filters: studies not related to the research topic, such as those with nonchronic kidney disease related vascular calcification or nonnutritional metabolic treatments, were excluded
Timeframe	2001–2022
Inclusion and exclusion criteria	Studies that focused on the effects of malnutrition or metabolic disorders on VC in CKD and the nutritional or metabolic treatments for CKD-VC were included. Studies that did not focus on this issue were excluded
Selection process	Articles retrieved from the searches were evaluated independently by two investigators (Yuqin Xiong and Yang Yu) using predefined forms, and any discrepancies were resolved by consensus after discussion with a third investigator (Baihai Su)

CKD, chronic kidney disease; VC, vascular calcification.

with increasing coronary artery calcification (CAC) scores showed an increased risk of cardiovascular disease (4). Thus, VC is deemed an independent risk factor for cardiovascular events and cardiac death in CKD patients (4-6).

Although the pathological mechanism underlying CKD-VC (oxidative/endoplasmic reticulum stress, autophagy inhibition, apoptosis, exosome vesicle release, and extracellular matrix remodelling) has been widely studied (1,7), treatments for CKD-VC based on inhibiting a single pathological pathway or target are difficult to restrain the development of VC. A recent systematic review of clinical trials showed that few interventions could attenuate VC progression in CKD with robust evidence (8). This treatment dilemma of CKD-VC may be because VC is regulated by multiple factors secondary to CKD. Herein, a narrative review was conducted on the pro-calcifying factors in the setting of CKD from the perspective of nutrition and metabolism. We present this article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5358/rc).

Methods

PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials were systematically searched for literature from 2001 as at July 26, 2022. Basic and clinical studies reporting the effects of malnutrition or metabolic disorders on VC in CKD and the evolving treatments for these nutrient metabolic disorders were selected and summarized (*Table 1* and Table S1).

Findings and discussion

Mineral metabolism disorder

Hyperphosphatemia

As CKD progresses to the end stage, phosphate excretion disorders and bone remodelling elevate the serum levels of phosphate. Clinical studies have shown that hyperphosphatemia is significantly and positively correlated with VC progression in hemodialysis (HD) patients (9-11). A relatively high serum phosphate concentration within the normal range (0.81 to 1.45 mmol/L) in patients with moderate CKD could still increase the risk of vascular and valvular calcification (10). Phosphate is a key component of hydroxyapatite crystals, which directly promotes apatite crystal deposition (7). *In vitro* studies have shown that phosphate induces VSMC calcification in a dose- and time-dependent manner (12,13). Phosphate is mediated in VSMCs by the type III sodium-dependent phosphate cotransporters Pit-1 and Pit-2. Upregulated Pit-1 increases the level of intracellular inorganic phosphate and enhances the osteogenic signal expression of Runt-

related transcription factor 2 (Runx2) and osteogenic transformation of VSMCs (12,14). When VSMCs are incubated with Pit-1 competitive inhibitors or Pit-1-silenced cells are incubated with a high-phosphate medium, phosphate uptake, osteogenic signal expression and calcification are significantly reduced (7,12).

Due to the adverse effects of high phosphate on cardiovascular outcomes, the Kidney Disease Improving Global Outcome (KDIGO) guidelines recommend limiting the dietary intake of phosphate in CKD stages 3–5 and dialysis-dependent (CKD5D) patients. This could be achieved by replacing animal-derived proteins with plant-derived proteins to reduce organophosphate intake and by avoiding inorganic phosphate intake from food additives (15,16). For patients who fail to obtain normal serum phosphate through dietary phosphate limits, phosphate-lowering agents are the mainstream treatment methods. In a meta-analysis, CKD stage 2–5 patients treated with lanthanum carbonate (4 studies, n=171), sevelamer (5 studies, n=483), and iron-based phosphate binders (3 studies, n=422) decreased mean blood phosphate levels to 0.48, 0.28, and 1.33 mg/dL, respectively, which were lower than those in the placebo group (17).

In addition to phosphate-lowering effects, iron-based phosphate binders (ferric citrate and sucroferric oxyhydroxide) downregulate the serum levels of fibroblast growth factor-23 (FGF23) and parathyroid hormone (PTH) in CKD patients (18-20). FGF23 is a phosphaturic hormone secreted from osteocytes/osteoblasts and maintains phosphate homeostasis by increasing renal phosphate excretion and decreasing the synthesis of 1,25-dihydroxyvitamin D and PTH (21). It is accepted that FGF23 levels are elevated in CKD and correlated with abnormal mineral metabolism, which may affect VC (21). There is evidence that FGF23 can directly act on vascular cells to promote or inhibit matrix calcification (22-24). Moreover, sucroferric oxyhydroxide, with a lower pill burden than sevelamer exerting a similar phosphate-lowering effect (decreased by 0.70±0.66 mmol/L over 1 year) in dialysis patients, was found to cause a significant decrease in tartrate-resistant acid phosphatase 5b and an increase in bone-specific alkaline phosphatase (ALP) and osteocalcin (20). Currently, the main concern regarding the use of iron-based phosphate binders in patients on dialysis is their effect on iron-related indicators, such as hemoglobin, serum levels of ferritin and transferrin saturation (25-28).

Although new phosphate binders show good phosphate-lowering effects and few adverse effects, as well as an ability to regulate the markers of calcium-phosphate and bone, there is no strong clinical evidence that phosphate binders delay VC or improve the long-term cardiovascular prognosis of CKD (17). A systematic review of 20 clinical trials, including 2,498 nondialysis CKD patients with a median follow-up period of 9 months, showed a 0.37 mg/dL decrease in the mean serum phosphate levels; however, it was observed in three of the trials (n=184, 9–24 months) that a significant increase of 0.47 mean standard deviation in CAC scores in the noncalcium-phosphate binder group than the placebo group (*Table 2*) (29). There are some limitations in the current studies: lack of a placebo-control group while evaluating phosphate-lowering treatment in dialysis patients, a short follow-up period, and a lack of endpoints related to VC, renal bone disease, or cardiovascular death.

Calcium load

In CKD stages 3–4, the ability of 25-dihydroxyvitamin D to hydroxylate into 1,25-dihydroxyvitamin D is weakened due to insufficient renal 1-hydroxylase synthesis, resulting in reduced calcium and phosphate reuptake in intestinal and renal tubules as well as reduced bone calcium and phosphate released into the circulation. Urinary calcium excretion decreases as a compensatory response to hypocalcemia secondary to CKD and may retain the serum calcium level in the normal range. In end-stage renal disease (ESRD), hypercalcemia or calcium overload may occur due to nondynamic bone disease or severe secondary hyperparathyroidism (so-called tertiary hyperparathyroidism) or an excessive use of calcium-phosphate binders or calcitriol. *In vitro* studies have shown that high serum calcium levels aggravate VSMC calcification induced by high phosphate via upregulated Pit-1 expression (44), increased matrix vesicle release, and enhanced hydroxyapatite deposition (7,45). A prospective multicenter controlled study based on CKD stages 3–4 showed that the calcium acetate group was more likely to develop hypercalcemia (78% *vs.* 5%, P<0.01) and had a higher incidence of CAC (81.8% *vs.* 12.8%) during the 2 years of follow-up than the sevelamer group (30) (*Table 2*). In a high phosphate environment, the relative increase in serum calcium levels also elevates the risk of vascular lesions in CKD (46,47). Notably, patients with ESRD and calcium overload did not exhibit hypercalcemia due to ectopic deposition of calcium (48). Guérin *et al.* and Chertow *et al.* reported that the prevalence of CAC was not remarkedly reduced in CKD patients with normal serum levels of calcium and phosphate (48,49). Thus, identifying and

Table 2 Summary of studies related to nutrient metabolic treatment of CKD-VC

Reference	Study subject (sample at baseline), follow-up period	Treatment/intervention	Control	Outcomes
Lioufas *et al.* (29), 2022	Patients with CKD stages 3–4 (n=184, 3 clinical trials), 9–24 months	Noncalcium-phosphate binder	Placebo	A significant increase of 0.47 mean standard deviation in CAC score was observed in phosphate binder groups
Di Iorio *et al.* (30), 2012	Patients with CKD stages 3–4 (n=212), 2 years	Sevelamer	Calcium acetate	A lower incidence of CAC was observed in the sevelamer group (12.8% versus 81.8%)
Zelt *et al.* (31), 2015	Adenine-induced CKD rats (n=32)	0.2% Mg diet	0.05% Mg diet	Attenuated VC was shown in the abdominal aorta (51% reduction), iliac (44%) and carotid (46%) arteries
Kaesler *et al.* (32), 2020	Subtotal nephrectomy-induced CKD mice (n=40)	3% $MgCO_3$ diet	No $MgCO_3$ diet	Attenuated VC was observed in the aorta heart, and kidney
Leenders *et al.* (33), 2022	Subtotal nephrectomy-induced CKD Rats (n=46)	0.48% Mg diet	0.05% Mg diet	Reduced VC was shown in the abdominal aorta, while not seen in aortic arch or thoracic aorta
Bressendorff *et al.* (34), 2017	Patients with CKD stages 3–4 (n=36), 8 weeks	Oral Mg supplements with elemental Mg of 15/30 mmol daily	Placebo	Serum calcification propensity assessed by serum T_{50} level was improved because the mean T_{50} increased significantly by 40 min in the Mg 30 mmol/day group
Sakaguchi *et al.* (35), 2019	Patients with CKD stages 3–4 (n=123), 2 years	Oral MgO, an initial dose of 330 mg (elemental Mg 198 mg/8.3 mmol daily) and then doses were adjusted every 1–3 months to achieve serum Mg levels of 2.5–3.0 mg/dL	Standard therapy for CKD alone	The median change in CAC score (11.3% versus 39.5%) and the proportion of patients with an annualized percentage change in CAC score of ≥15% (23.9% versus 62.0%) were significantly lower in the MgO group
Bressendorff *et al.* (36), 2018	Patients on maintenance hemodialysis (n=59), 28 days	Dialysate Mg concentration of 2.0 mEq/L	Standard dialysate Mg concentration of 1.0 mEq/L	Serum calcification propensity assessed by serum T_{50} level was significantly improved in the high dialysate Mg group (mean T_{50} increased by 55 min), while had no significant change in control (decreased by 4 min)
Seto *et al.* (37), 2014	Adenine-induced CKD rats (n=32)	Iron dextran was administered intraperitoneally once a week	Sterile saline administration	VC development was suppressed in the iron dextran group
Yamada *et al.* (38), 2015	Adenine-induced CKD rats (n=40)	Low-protein (9.5%) high-phosphate (1.2%) diet	Normal-protein (19%) high-phosphate (1.2%) diet	More calcified nodules and severer calcium content in the aorta was observed in the low-protein group
Price *et al.* (39), 2006	Adenine-induced CKD rats (n=47)	Low-protein (2.5% diet	Normal protein (25%) diet	More calcified nodules and severer calcium content in the aorta was observed in the low-protein group
Neradova *et al.* (40), 2022	Subtotal nephrectomy-induced CKD rats (n=90)	High-vitK2, high-phosphate diet	Low-vitK2, high-phosphate diet	The treatment combined a high vitK2 diet with phosphate binders significantly attenuated VC in thoracic and abdominal aortas

Table 2 (*continued*)

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Reference	Study subject (sample at baseline), follow-up period	Treatment/intervention	Control	Outcomes
Witham *et al.* (41), 2020	Patients with CKD stages 3b–4 (n=159), 1 year	Oral vitK2, 400 μg daily	Placebo	No detectable effect of vitK2 supplementation on VC markers
De Vriese *et al.* (42), 2020	Patients on maintenance hemodialysis (n=132), 18 months	Rivaroxaban 10 mg daily plus vitK2 2,000 μg thrice weekly	Rivaroxaban 10 mg daily	High-dose vitK2 have no significant favorable effect on VC progression
Oikonomaki *et al.* (43), 2019	Patients on maintenance hemodialysis (n=102), 1 year	Oral vitK2, 200 μg daily	No treatment	Abdominal aortic calcification score was increased significantly both in vitK2 and control groups and has no difference between the two groups

CKD, chronic kidney disease; VC, vascular calcification; CAC, coronary artery calcification; Mg, magnesium; MgO, magnesium oxide; vitK2, vitamin K2.

preventing calcium overload at an early stage is critical to the prevention and treatment of CKD-VC.

Hypomagnesemia

Magnesium balance depends on dietary intake and absorption, deposition and release of bone and soft tissue, and renal excretion. Hypermagnesemia often occurs in CKD stages 4–5 [glomerular filtration rate (GFR) <30 mL/minute] because magnesium excretion decreases even though fractional excretion of magnesium increases (50). In dialysis patients, the serum magnesium concentration is dependent on the dialysate magnesium concentration (51). Recent studies have shown that magnesium ions affect VC development by regulating the maturation of primary calciprotein particles (CPP1) and the mineralization of the extracellular matrix (52-55). Calciprotein particles (CPPs) are calcium-phosphate precipitated microparticles bound to the serum protein fetuin-A (Fet-A) that spontaneously generated in solution containing calcium, phosphate, and Fet-A to be dispersed in the blood. In contrast to amorphous soluble calcium-phosphate particles (CPP1), crystalline secondary calcium-phosphate particles (CPP2) have been shown to upregulate the expression of osteogenic proteins in VSMCs (53,56) and directly induce VSMC calcification (57). CPPs are increased in patients with CKD, and the transition from CPP1 towards CPP2 is regarded as the key pathological process that mediates inflammatory reactions and VC (56-58).

In vitro studies have shown that magnesium prevents phosphate-induced VSMC calcification by inhibiting CPP1 maturation and osteogenesis signal expression (53,54). In wild-type animal models of CKD, increasing the dietary magnesium concentration (0.2–0.48%) reduced the severity of VC (31-33) (*Table 2*). In klotho-knockout mice, dietary magnesium supplementation (0.48%) alleviated high phosphate-induced VC by inhibiting signal activation of aortic inflammation, osteogenesis, and extracellular matrix remodelling (55). In addition, magnesium inhibits the secretion of PTH and delays the progression of VC by activating the calcium-sensitive receptor of the parathyroid gland (59,60).

There are growing clinical studies supporting the protective role of magnesium on VC. In 100 nondialysis CKD stage 5 patients with a mean serum magnesium concentration of 0.82 mmol/L, the serum magnesium levels were negatively correlated with the degree of abdominal aortic calcification (61). Small sample clinical studies have shown that oral magnesium supplements delay CAC progression in patients with moderate-to-severe CKD (34,35). In 59 maintenance HD (MHD) patients, increased dialysate magnesium concentration (0.5 *vs.* 1.0 mmol/L) during a 28-day HD period increased the serum level of T_{50} (T_{50} refers to the maturation time from CPP1 to CPP2; a short T_{50} represents a significant risk for VC) (36,62) (*Table 2*). In conclusion, magnesium supplementation may be a new method for preventing and treating CKD-VC. The target serum magnesium level for each stage of CKD and the impact of magnesium supplementation on long-term prognosis need to be investigated further.

Iron deficiency

CKD is often associated with varying degrees of iron deficiency. Hepcidin is a small peptide hormone from the liver that inhibits iron absorption in the basement

membrane of intestinal epithelial cells and liver cells. The chronic inflammation in CKD (via cytokines and bacterial lipopolysaccharide) upregulates the expression and production of hepcidin, which results in functional iron deficiency (enhanced ferritin, diminished transferrin production and iron availability), shunting iron to the reticuloendothelial storage pool instead of delivery to erythrocyte precursors. Additionally, inadequate renal erythropoietin synthesis and iron loss resulting from dialysis circulation can exacerbate iron deficiency (63). Mizuiri *et al.* have shown that iron deficiency (transferrin saturation <21%) in dialysis patients is an independent predictor for CAC scores >400 and is associated with poor cardiovascular outcomes (64). Iron ions bind with phosphate to inhibit phosphate transport into VSMCs, downregulate ALP activity in VSMCs, inhibit apoptosis, and enhance autophagy to suppress calcium deposition and cell phenotypic transformation, thereby inhibiting VC (65-67). Also, Seto *et al.* have confirmed that iron dextran delays the progression of VC in uremic rats by downregulating the expression of Pit-1 and Runx2 (37) (*Table 2*). Therefore, correction of iron deficiency might be beneficial for the prevention and treatment of VC. Furthermore, since iron can receive and transfer electrons, its overload can cause severe oxidative stress and tissue damage (68). Thus, the effects of iron supplementation on VC in CKD patients as well as an effective and safe dose of iron supplements need to be elucidated.

Dyslipidemia

Patients with CKD often have lipid abnormalities due to renal excretion disorders and deficient lipid metabolism enzyme activity, which manifests as increased levels of serum triglycerides, low-density lipoprotein cholesterol (LDL-C), lipoprotein(a) [Lp(a)], and monounsaturated fatty acids and decreased levels of high-density lipoprotein cholesterol and polyunsaturated fatty acids (69). Lp(a) is a lipoprotein particle that has a potential role as the main carrier of oxidized phospholipids that exhibit proinflammatory and procalcification effects (70,71). Recent studies suggested that increased Lp(a) levels are closely related to the risk of atherosclerosis and coronary stenosis in patients with CKD (72,73). *In vitro* studies have shown that Lp(a) mediates VC by activating the Notch1-NF-κB and Notch1-BMP2-Smad1/5/9 pathways (71), inducing calcified extracellular vesicle release (74), upregulating ALP activity and promoting calcium accumulation (75).

As the most widely used lipid-lowering agent, statins decrease LDL-C levels but either increase or have no effect on Lp(a) levels (76). Proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i, e.g., alirocumab and evolocumab) is a promising lipid-lowering agent developed recently (77,78). The mechanism underlying the PCSK9i-mediated correction of dyslipidemia is related to an inducing effect of PCSK9 mutation on LDL metabolism and hypercholesterolemia (79,80). In eight randomized controlled phase 3 ODYSSEY trials (double-blind treatments of 24–104 weeks) involving 4,629 hypercholesterolemic individuals without (89.9%) or with impaired renal function (10.1%), alirocumab decreased the serum Lp(a) level by 22.7–29.7% from baseline (81). The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial recruited 8,077 patients with preserved kidney function, 15,034 with stage 2 CKD, and 4,443 with stage 3 CKD and observed that the serum level of Lp(a) decreased with evolocumab from baseline at 48 weeks across CKD groups was 33%, 34%, and 34%, respectively (82). These findings confirmed the Lp(a)-lowering efficacy of PCSK9i in CKD patients, while the effect of PCSK9i on CKD-VC needs to be further elucidated.

Protein malnutrition

The recent KDIGO [2020] guidelines suggest that protein intake should be ≤0.6 g/kg/day for nondialysis CKD stages 3–5 patients and 1–1.2 g/kg/day for dialysis patients (83). However, there are no recommendations about protein intake related to VC prevention in CKD patients. A low-protein diet is one of the strategies to delay the progression of CKD, but excessive protein restriction often leads to protein malnutrition. A meta-analysis of studies published during 2000–2014 showed that 1,776 patients with CKD stages 3–5 had a protein-energy wasting (PEW) ranging from 11–54%; 16,434 MHD patients from 90 studies across 34 countries had a PEW prevalence of 28–54% in the 25th–75th percentile (84). A multicenter study published in 2018 showed a cooccurrence of inflammation and protein-calorie malnutrition in 11% of 98 MHD patients (85). Malnutrition is closely related to inflammation and atherosclerosis/calcification, which is defined as malnutrition inflammation atherosclerosis syndrome (86). *In vivo* studies have shown that uremic rats with a low-protein (2.5% or 9.5%) diet had more severe calcification in the media of the artery than those with a normal protein (19% or 25%) diet (38,39)

(*Table 2*). Protein restriction has a potential phosphate-lowering benefit, but it concurrently reduces the synthesis of calcification inhibitors, such as Fet-A and matrix Gla protein (MGP). Downregulated calcification inhibitors, together with systemic inflammation and oxidative stress secondary to malnutrition, promote VC development (38,39,87). Therefore, the current adherence to dietary recommendations in patients with CKD and the minimum protein intake for not increasing the risk of VC need to be further identified.

Vitamin K deficiency

Vitamin K deficiency is common in patients with CKD. According to the National Health and Nutrition Survey in the US, the average intake of vitamin K1 in adults with CKD is 97.5 μg/day, and >72% of patients do not reach the recommended intake (88). A survey from Italy showed that the median intake of vitamin K1 in HD adults was 71.6 μg/day, and >80% of patients did not meet the national recommended intake (89). Vitamin K deficiency in CKD might be related to dietary potassium restriction since most potassium-rich vegetables are also rich in vitamin K. Additionally, inhibition of vitamin K activase expression and activity due to CKD and the use of vitamin K antagonists such as warfarin could lead to vitamin K deficiency (90).

Vitamin K regulates the development of VC by vitamin K-dependent proteins that have calcification-inhibiting effects, such as MGP and plasma-free protein S (91). Warfarin increases calcium deposition in the thoracic and abdominal aortas of uremic rats, which can be ameliorated by high doses of vitamin K2 (40) (*Table 2*). Consistent with *in vivo* studies, clinical studies have shown that warfarin significantly increases the occurrence and progression of VC (92,93). Although a post hoc analysis of the ViKCoVaC (effect of Vitamin-K1 and Colchicine on Vascular Calcification activity in subjects with Diabetes Mellitus) double-blind randomized controlled trial showed that vitamin K1 supplements (10 mg/day) delay the progression of CAC in diabetic patients (94), clinical evidence for VC delay in CKD patients is scarce. In a clinical trial, Westenfeld *et al.* reported that vitamin K2 supplementation is beneficial for increasing the level of active MGP in 53 HD patients (95). Conversely, three clinical trials demonstrated that vitamin K2 supplementation could not delay the progression of atherosclerosis or VC in 159 patients with CKD stages 3–4, 132 HD patients or 102 HD patients (41-43) (*Table 2*). Additionally, the cardiovascular benefits of vitamin K1 supplementation in CKD patients need to be clarified.

Conclusions

VC is a common and refractory complication of CKD with a poor prognosis. Factors secondary to CKD, including hyperphosphatemia, calcium load, hypomagnesemia, iron deficiency, lipoprotein(a) abnormalities, protein malnutrition, and vitamin K deficiency, are the "natural medium" for the progression of VC. Additional studies are needed to address optimal nutrition strategies for preventing and delaying VC development in patients with CKD.

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Footnote

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References

1. Thompson B, Towler DA. Arterial calcification and bone physiology: role of the bone-vascular axis. Nat Rev Endocrinol 2012;8:529-43.
2. Nam SH, Kang SG, Song SW. The Neutrophil-Lymphocyte Ratio Is Associated with Coronary Artery Calcification in Asymptomatic Korean Males: A Cross-Sectional Study. Biomed Res Int 2017;2017:1989417.
3. Xiong Y, Li J, Sun S, et al. Association of mineral content outside of bone with coronary artery calcium and 1-year cardiovascular prognosis in maintenance hemodialysis patients. Artif Organs 2019;43:988-1001.
4. Chen J, Budoff MJ, Reilly MP, et al. Coronary Artery Calcification and Risk of Cardiovascular Disease and Death Among Patients With Chronic Kidney Disease. JAMA Cardiol 2017;2:635-43.
5. Budoff MJ, Rader DJ, Reilly MP, et al. Relationship of estimated GFR and coronary artery calcification in the CRIC (Chronic Renal Insufficiency Cohort) Study. Am J Kidney Dis 2011;58:519-26.
6. Budoff MJ, Young R, Lopez VA, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2013;61:1231-9.
7. Lee SJ, Lee IK, Jeon JH. Vascular Calcification-New Insights Into Its Mechanism. Int J Mol Sci 2020;21:2685.
8. Xu C, Smith ER, Tiong MK, et al. Interventions To Attenuate Vascular Calcification Progression in Chronic Kidney Disease: A Systematic Review of Clinical Trials. J Am Soc Nephrol 2022;33:1011-32.
9. Chertow GM, Raggi P, Chasan-Taber S, et al. Determinants of progressive vascular calcification in haemodialysis patients. Nephrol Dial Transplant 2004;19:1489-96.
10. Adeney KL, Siscovick DS, Ix JH, et al. Association of serum phosphate with vascular and valvular calcification in moderate CKD. J Am Soc Nephrol 2009;20:381-7.
11. Wang XR, Yuan L, Shi R, et al. Predictors of coronary artery calcification and its association with cardiovascular events in patients with chronic kidney disease. Ren Fail 2021;43:1172-9.
12. Chavkin NW, Chia JJ, Crouthamel MH, et al. Phosphate uptake-independent signaling functions of the type III sodium-dependent phosphate transporter, PiT-1, in vascular smooth muscle cells. Exp Cell Res 2015;333:39-48.
13. Wen P, Cao H, Fang L, et al. miR-125b/Ets1 axis regulates transdifferentiation and calcification of vascular smooth muscle cells in a high-phosphate environment. Exp Cell Res 2014;322:302-12.
14. Ding M, Zhang Q, Zhang M, et al. Phosphate Overload Stimulates Inflammatory Reaction via PiT-1 and Induces Vascular Calcification in Uremia. J Ren Nutr 2022;32:178-88.
15. Moe SM, Zidehsarai MP, Chambers MA, et al. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. Clin J Am Soc Nephrol 2011;6:257-64.
16. Garcia-Torres R, Young L, Murray DP, et al. Dietary Protein Source and Phosphate Levels in Patients on Hemodialysis. J Ren Nutr 2020;30:423-9.
17. Ruospo M, Palmer SC, Natale P, et al. Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD). Cochrane Database Syst Rev 2018;8:CD006023.
18. Block GA, Pergola PE, Fishbane S, et al. Effect of ferric citrate on serum phosphate and fibroblast growth factor 23 among patients with nondialysis-dependent chronic kidney disease: path analyses. Nephrol Dial Transplant 2019;34:1115-24.
19. Yokoyama K, Hirakata H, Akiba T, et al. Ferric citrate hydrate for the treatment of hyperphosphatemia in nondialysis-dependent CKD. Clin J Am Soc Nephrol 2014;9:543-52.
20. Ketteler M, Sprague SM, Covic AC, et al. Effects of sucroferric oxyhydroxide and sevelamer carbonate on chronic kidney disease-mineral bone disorder parameters in dialysis patients. Nephrol Dial Transplant 2019;34:1163-70.
21. Yamada S, Giachelli CM. Vascular calcification in CKD-MBD: Roles for phosphate, FGF23, and Klotho. Bone 2017;100:87-93.
22. Nakahara T, Kawai-Kowase K, Matsui H, et al. Fibroblast growth factor 23 inhibits osteoblastic gene expression and induces osteoprotegerin in vascular smooth muscle cells. Atherosclerosis 2016;253:102-10.
23. Lim K, Lu TS, Molostvov G, et al. Vascular Klotho

deficiency potentiates the development of human artery calcification and mediates resistance to fibroblast growth factor 23. Circulation 2012;125:2243-55.
24. Jimbo R, Kawakami-Mori F, Mu S, et al. Fibroblast growth factor 23 accelerates phosphate-induced vascular calcification in the absence of Klotho deficiency. Kidney Int 2014;85:1103-11.
25. Lewis JB, Sika M, Koury MJ, et al. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. J Am Soc Nephrol 2015;26:493-503.
26. Lioulios G, Stangou M, Sarafidis PA, et al. Chronic Therapy with Sucroferric Oxyhydroxide Does Not Affect Iron and Anemia Markers in Dialysis Patients. Blood Purif 2020;49:440-7.
27. Covic AC, Floege J, Ketteler M, et al. Iron-related parameters in dialysis patients treated with sucroferric oxyhydroxide. Nephrol Dial Transplant 2017;32:1330-8.
28. Floege J, Covic AC, Ketteler M, et al. Long-term effects of the iron-based phosphate binder, sucroferric oxyhydroxide, in dialysis patients. Nephrol Dial Transplant 2015;30:1037-46.
29. Lioufas NM, Pascoe EM, Hawley CM, et al. Systematic Review and Meta-Analyses of the Effects of Phosphate-Lowering Agents in Nondialysis CKD. J Am Soc Nephrol 2022;33:59-76.
30. Di Iorio B, Bellasi A, Russo D, et al. Mortality in kidney disease patients treated with phosphate binders: a randomized study. Clin J Am Soc Nephrol 2012;7:487-93.
31. Zelt JG, McCabe KM, Svajger B, et al. Magnesium Modifies the Impact of Calcitriol Treatment on Vascular Calcification in Experimental Chronic Kidney Disease. J Pharmacol Exp Ther 2015;355:451-62.
32. Kaesler N, Goettsch C, Weis D, et al. Magnesium but not nicotinamide prevents vascular calcification in experimental uraemia. Nephrol Dial Transplant 2020;35:65-73.
33. Leenders NHJ, Bos C, Hoekstra T, et al. Dietary magnesium supplementation inhibits abdominal vascular calcification in an experimental animal model of chronic kidney disease. Nephrol Dial Transplant 2022;37:1049-58.
34. Bressendorff I, Hansen D, Schou M, et al. Oral Magnesium Supplementation in Chronic Kidney Disease Stages 3 and 4: Efficacy, Safety, and Effect on Serum Calcification Propensity-A Prospective Randomized Double-Blinded Placebo-Controlled Clinical Trial. Kidney Int Rep 2017;2:380-9.
35. Sakaguchi Y, Hamano T, Obi Y, et al. A Randomized Trial of Magnesium Oxide and Oral Carbon Adsorbent for Coronary Artery Calcification in Predialysis CKD. J Am Soc Nephrol 2019;30:1073-85.
36. Bressendorff I, Hansen D, Schou M, et al. The Effect of Increasing Dialysate Magnesium on Serum Calcification Propensity in Subjects with End Stage Kidney Disease: A Randomized, Controlled Clinical Trial. Clin J Am Soc Nephrol 2018;13:1373-80.
37. Seto T, Hamada C, Tomino Y. Suppressive effects of iron overloading on vascular calcification in uremic rats. J Nephrol 2014;27:135-42.
38. Yamada S, Tokumoto M, Tsuruya K, et al. Fetuin-A decrease induced by a low-protein diet enhances vascular calcification in uremic rats with hyperphosphatemia. Am J Physiol Renal Physiol 2015;309:F744-54.
39. Price PA, Roublick AM, Williamson MK. Artery calcification in uremic rats is increased by a low protein diet and prevented by treatment with ibandronate. Kidney Int 2006;70:1577-83.
40. Neradova A, Wasilewski G, Prisco S, et al. Combining phosphate binder therapy with vitamin K2 inhibits vascular calcification in an experimental animal model of kidney failure. Nephrol Dial Transplant 2022;37:652-62.
41. Witham MD, Lees JS, White M, et al. Vitamin K Supplementation to Improve Vascular Stiffness in CKD: The K4Kidneys Randomized Controlled Trial. J Am Soc Nephrol 2020;31:2434-45.
42. De Vriese AS, Caluwé R, Pyfferoen L, et al. Multicenter Randomized Controlled Trial of Vitamin K Antagonist Replacement by Rivaroxaban with or without Vitamin K2 in Hemodialysis Patients with Atrial Fibrillation: the Valkyrie Study. J Am Soc Nephrol 2020;31:186-96.
43. Oikonomaki T, Papasotiriou M, Ntrinias T, et al. The effect of vitamin K2 supplementation on vascular calcification in haemodialysis patients: a 1-year follow-up randomized trial. Int Urol Nephrol 2019;51:2037-44.
44. Masumoto A, Sonou T, Ohya M, et al. Calcium Overload Accelerates Phosphate-Induced Vascular Calcification Via Pit-1, but not the Calcium-Sensing Receptor. J Atheroscler Thromb 2017;24:716-24.
45. Nguyen NT, Nguyen TT, Da Ly D, et al. Oxidative stress by Ca(2+) overload is critical for phosphate-induced vascular calcification. Am J Physiol Heart Circ Physiol 2020;319:H1302-12.
46. Moe SM. Calcium as a cardiovascular toxin in CKD-MBD. Bone 2017;100:94-9.
47. Young EW, Akiba T, Albert JM, et al. Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 2004;44:34-8.

48. Guérin AP, London GM, Marchais SJ, et al. Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplant 2000;15:1014-21.
49. Chertow GM, Burke SK, Raggi P, et al. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002;62:245-52.
50. Felsenfeld AJ, Levine BS, Rodriguez M. Pathophysiology of Calcium, Phosphorus, and Magnesium Dysregulation in Chronic Kidney Disease. Semin Dial 2015;28:564-77.
51. Cunningham J, Rodríguez M, Messa P. Magnesium in chronic kidney disease Stages 3 and 4 and in dialysis patients. Clin Kidney J 2012;5:i39-51.
52. Ter Braake AD, Vervloet MG, de Baaij JHF, et al. Magnesium to prevent kidney disease-associated vascular calcification: crystal clear? Nephrol Dial Transplant 2022;37:421-9.
53. Ter Braake AD, Eelderink C, Zeper LW, et al. Calciprotein particle inhibition explains magnesium-mediated protection against vascular calcification. Nephrol Dial Transplant 2020;35:765-73.
54. Zhu X, Ma K, Zhou K, et al. Reversal of phosphate-induced ORAI1 expression, store-operated Ca(2+) entry and osteogenic signaling by MgCl(2) in human aortic smooth muscle cells. Biochem Biophys Res Commun 2020;523:18-24.
55. Ter Braake AD, Smit AE, Bos C, et al. Magnesium prevents vascular calcification in Klotho deficiency. Kidney Int 2020;97:487-501.
56. Sage AP, Lu J, Tintut Y, et al. Hyperphosphatemia-induced nanocrystals upregulate the expression of bone morphogenetic protein-2 and osteopontin genes in mouse smooth muscle cells in vitro. Kidney Int 2011;79:414-22.
57. Aghagolzadeh P, Bachtler M, Bijarnia R, et al. Calcification of vascular smooth muscle cells is induced by secondary calciprotein particles and enhanced by tumor necrosis factor-α. Atherosclerosis 2016;251:404-14.
58. Akiyama KI, Miura Y, Hayashi H, et al. Calciprotein particles regulate fibroblast growth factor-23 expression in osteoblasts. Kidney Int 2020;97:702-12.
59. Massy ZA, Drüeke TB. Magnesium and outcomes in patients with chronic kidney disease: focus on vascular calcification, atherosclerosis and survival. Clin Kidney J 2012;5:i52-61.
60. Apetrii M, Covic A, Massy ZA. Magnesium supplementation: A consideration in dialysis patients. Semin Dial 2018;31:11-4.
61. Ito M, Yamaguchi M, Katsuno T, et al. Association between serum magnesium levels and abdominal aorta calcification in patients with pre-dialysis chronic kidney disease stage 5. PLoS One 2021;16:e0253592.
62. Bressendorff I, Hansen D, Pasch A, et al. The effect of increasing dialysate magnesium on calciprotein particles, inflammation and bone markers: post hoc analysis from a randomized controlled clinical trial. Nephrol Dial Transplant 2021;36:713-21.
63. Gluba-Brzózka A, Franczyk B, Olszewski R, et al. The Influence of Inflammation on Anemia in CKD Patients. Int J Mol Sci 2020;21:725.
64. Mizuiri S, Nishizawa Y, Doi T, et al. Iron, coronary artery calcification, and mortality in patients undergoing hemodialysis. Ren Fail 2021;43:371-80.
65. Becs G, Zarjou A, Agarwal A, et al. Pharmacological induction of ferritin prevents osteoblastic transformation of smooth muscle cells. J Cell Mol Med 2016;20:217-30.
66. Zarjou A, Jeney V, Arosio P, et al. Ferritin prevents calcification and osteoblastic differentiation of vascular smooth muscle cells. J Am Soc Nephrol 2009;20:1254-63.
67. Ciceri P, Falleni M, Tosi D, et al. Therapeutic Effect of Iron Citrate in Blocking Calcium Deposition in High Pi-Calcified VSMC: Role of Autophagy and Apoptosis. Int J Mol Sci 2019;20:5925.
68. Sumneang N, Siri-Angkul N, Kumfu S, et al. The effects of iron overload on mitochondrial function, mitochondrial dynamics, and ferroptosis in cardiomyocytes. Arch Biochem Biophys 2020;680:108241.
69. Kochan Z, Szupryczynska N, Malgorzewicz S, et al. Dietary Lipids and Dyslipidemia in Chronic Kidney Disease. Nutrients 2021;13:3138.
70. Zheng KH, Tsimikas S, Pawade T, et al. Lipoprotein(a) and Oxidized Phospholipids Promote Valve Calcification in Patients With Aortic Stenosis. J Am Coll Cardiol 2019;73:2150-62.
71. Peng J, Liu MM, Liu HH, et al. Lipoprotein (a)-mediated vascular calcification: population-based and in vitro studies. Metabolism 2022;127:154960.
72. Bermudez-Lopez M, Forne C, Amigo N, et al. An in-depth analysis shows a hidden atherogenic lipoprotein profile in non-diabetic chronic kidney disease patients. Expert Opin Ther Targets 2019;23:619-30.
73. Lin LH, Liu H, Tu Y, et al. Association of lipoprotein(a) and coronary artery disease in 1003 patients with stage 3-5 chronic kidney disease undergoing coronary angiography. Coron Artery Dis 2019;30:137-42.
74. Rogers MA, Atkins SK, Zheng KH, et al. Lipoprotein(a) Induces Vesicular Cardiovascular Calcification Revealed

With Single-Extracellular Vesicle Analysis. Front Cardiovasc Med 2022;9:778919.
75. Sun H, Unoki H, Wang X, et al. Lipoprotein(a) enhances advanced atherosclerosis and vascular calcification in WHHL transgenic rabbits expressing human apolipoprotein(a). J Biol Chem 2002;277:47486-92.
76. Tsimikas S, Gordts PLSM, Nora C, et al. Statin therapy increases lipoprotein(a) levels. Eur Heart J 2020;41:2275-84.
77. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med 2018;379:2097-107.
78. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017;376:1713-22.
79. Abifadel M, Varret M, Rabès JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 2003;34:154-6.
80. Li J, Tumanut C, Gavigan JA, et al. Secreted PCSK9 promotes LDL receptor degradation independently of proteolytic activity. Biochem J 2007;406:203-7.
81. Toth PP, Dwyer JP, Cannon CP, et al. Efficacy and safety of lipid lowering by alirocumab in chronic kidney disease. Kidney Int 2018;93:1397-408.
82. Charytan DM, Sabatine MS, Pedersen TR, et al. Efficacy and Safety of Evolocumab in Chronic Kidney Disease in the FOURIER Trial. J Am Coll Cardiol 2019;73:2961-70.
83. Ikizler TA, Burrowes JD, Byham-Gray LD, et al. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. Am J Kidney Dis 2020;76:S1-S107.
84. Carrero JJ, Thomas F, Nagy K, et al. Global Prevalence of Protein-Energy Wasting in Kidney Disease: A Meta-analysis of Contemporary Observational Studies From the International Society of Renal Nutrition and Metabolism. J Ren Nutr 2018;28:380-92.
85. Maraj M, Kuśnierz-Cabala B, Dumnicka P, et al. Malnutrition, Inflammation, Atherosclerosis Syndrome (MIA) and Diet Recommendations among End-Stage Renal Disease Patients Treated with Maintenance Hemodialysis. Nutrients 2018;10:69.
86. Yamada S, Tsuruya K, Kitazono T, et al. Emerging cross-talks between chronic kidney disease-mineral and bone disorder (CKD-MBD) and malnutrition-inflammation complex syndrome (MICS) in patients receiving dialysis. Clin Exp Nephrol 2022;26:613-29.
87. Mutluay R, Konca Değertekin C, Işıktaş Sayılar E, et al. Serum fetuin-A is associated with the components of MIAC(malnutrition, inflammation, atherosclerosis, calcification) syndrome in different stages of chronic kidney disease. Turk J Med Sci 2019;49:327-35.
88. Cheung CL, Sahni S, Cheung BM, et al. Vitamin K intake and mortality in people with chronic kidney disease from NHANES III. Clin Nutr 2015;34:235-40.
89. Fusaro M, D'Alessandro C, Noale M, et al. Low vitamin K1 intake in haemodialysis patients. Clin Nutr 2017;36:601-7.
90. McCabe KM, Booth SL, Fu X, et al. Vitamin K Metabolism in a Rat Model of Chronic Kidney Disease. Am J Nephrol 2017;45:4-13.
91. Tesfamariam B. Involvement of Vitamin K-Dependent Proteins in Vascular Calcification. J Cardiovasc Pharmacol Ther 2019;24:323-33.
92. Nuotio K, Koskinen SM, Mäkitie L, et al. Warfarin Treatment Is Associated to Increased Internal Carotid Artery Calcification. Front Neurol 2021;12:696244.
93. Andrews J, Psaltis PJ, Bayturan O, et al. Warfarin Use Is Associated With Progressive Coronary Arterial Calcification: Insights From Serial Intravascular Ultrasound. JACC Cardiovasc Imaging 2018;11:1315-23.
94. Bellinge JW, Francis RJ, Lee SC, et al. The effect of vitamin K1 on arterial calcification activity in subjects with diabetes mellitus: a post hoc analysis of a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr 2022;115:45-52.
95. Westenfeld R, Krueger T, Schlieper G, et al. Effect of vitamin K2 supplementation on functional vitamin K deficiency in hemodialysis patients: a randomized trial. Am J Kidney Dis 2012;59:186-95.

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Supplementary

Table S1 The detailed search strategy (taking PubMed as an example)

Items	Specification
MeSH	(("Vascular Calcification/diet therapy"[Mesh]) OR "Vascular Calcification/metabolism"[Mesh]) OR "Vascular Calcification/prevention and control"[Mesh]. 1,633 references were found and evaluated according to the inclusion and exclusion criteria, and 25 references were included in this study
Free text	Chronic Kidney Disease; Vascular Calcification; Artery Calcification; Phosphate; Phosphate-Lowering Agents; Ferric Citrate; Sucroferric Oxyhydroxide; Calcium; Magnesium; Iron; Dyslipidemia; Low-Density Lipoprotein Cholesterol; Lipoprotein(a); Malnutrition; Vitamin K
Filters	Studies not related to the research topic, such as those with nonchronic kidney disease related vascular calcification or nonnutritional metabolic treatments, were excluded

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