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, and the Cochrane Central Register of Controlled Trials) 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 Central Register of Controlled Trials
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% *vs.* 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% *vs.* 39.5%) and the proportion of patients with an annualized percentage change in CAC score of ≥15% (23.9% *vs.* 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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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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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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