Review Article

Vitamin K and vascular calcification in chronic kidney disease: An update of current evidence

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Abstract

Vascular calcification, characterized by calcium deposition in the intimal and medial layers of the arterial wall, is frequently encountered in patients with chronic kidney disease (CKD) and leads to an enhanced risk of adverse cardiovascular (CV) outcomes. However, the underlying complex pathophysiology remains incompletely understood. Recently, Vitamin K supplementation aimed at correcting Vitamin K deficiency highly prevalent in CKD holds great promise to mitigate the progression of vascular calcification. This article discusses the functional Vitamin K status in CKD, the pathophysiology linking Vitamin K deficiency and vascular calcification, and reviews current literature from animal models, observational studies, and clinical trials across the different spectrum of CKD. While favorable effects of Vitamin K on vascular calcification and CV outcomes are suggested in animal and observational studies, most recently published clinical trials investigating the effects of Vitamin K on vascular health failed to support the beneficial role of Vitamin K supplementation, despite improving the functional status of Vitamin K. We address the potential reasons for these discrepancies and provide further perspective on Vitamin K research in CKD.

Keywords: *Arterial stiffness, Chronic kidney disease, Matrix Gla-protein, Vascular calcification, Vitamin K*

Introduction

*C*ardiovascular (CV) disease is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) [1]. Several cardiac and vascular abnormalities are demonstrated to account for this increased risk of CV events and mortality. Identifying modifiable risk factors that contribute to the development of CV disease in CKD is particularly important. Beyond the well-established traditional risk factors, such as aging, diabetic mellitus, hypertension, hyperlipidemia, smoking, and obesity, several nontraditional risk factors, including dysregulation of fibroblast growth factors-23 and klotho, deposition of calcium and phosphorus, endothelial dysfunction, chronic inflammation, oxidative stress, gut-derived uremic toxins, and malnutrition, were also implicated in the pathogenesis of CV disease [2,3].

Vascular calcification, characterized by calcium deposition in the intimal and medial layers of the arterial wall, is one of the most special and relevant contributors responsible for the high CV burden in patients with CKD and ESRD [4]. However, the pathophysiology of this accelerated and extensive vascular calcification in CKD remains not completely understood, and a large body of research is ongoing to elucidate the complex pathogenesis.

Notably, growing evidence suggests a close association between Vitamin K deficiency and accelerated vascular calcification, which has drawn significant attention from researchers in recent years [5-9]. And Vitamin K supplementation is regarded as a promising approach to mitigate the progression of vascular calcification in CKD patients.

This review addressed and updated current evidence regarding the role of Vitamin K on vascular calcification in CKD from experimental animal models, observational, and clinical trials.

Sources, bioabsorption, and function of Vitamin K

The Vitamin K family members, which share a naphthoquinone double ring in structure, are comprised of

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Vitamin K_1 (phylloquinone) and Vitamin K_2 (menaquinones, MKs), the latter of which includes MK-4 through to MK-13, named depending on the length of lipophilic isoprenoid side chain [10]. Among menaquinones, two isoforms, MK-4 and MK-7, are available in supplement form. As an essential micronutrient that needs to intake through food, Vitamin K_1 is abundant in leafy green vegetables (such as spinach, broccoli, Brussels sprouts, cabbage, and kale), MK-4 is rich in Butter, eggs yolks, and animal-based foods, and MK-7 is derived from fermented food, such as Natto and cheeses [11,12]. In general, Vitamin K_1 is more abundant in foods and accounts for the majority of Vitamin K intake in the human diet. Following oral intake, Vitamin K_1 and K_2 are absorbed via the small intestine, packed into the chylomicrons, and then transported to tissue by lipoproteins. Vitamin K_1 is mainly accumulated in the liver and is responsible for coagulation function, whereas Vitamin K_2 exerts a more extrahepatic distribution pattern and is believed to have diverse impacts on human health [13]. Notably, an adequate intake of Vitamin K_2, but not Vitamin K_1, is associated with a reduced risk of coronary heart disease [14].

Vitamin K is a crucial cofactor for various Vitamin K-dependent proteins in the body. In humans, at least 17 different Vitamin K-dependent proteins have been identified [10]. Apart from hemostasis function as the most well-known biological function of Vitamin K, emerging evidence suggests that this micronutrient is also implicated in diverse biological functions, such as CV and renal protection, bone health, glycemic control, cognitive function, and cancer prevention [12,15].

Vitamin K status in chronic kidney disease

Insufficient Vitamin K intake, as well as hypofunction of Vitamin K status, is commonly observed in CKD. Based on the Third National Health and Nutrition Examination Survey (NHANES III), up to 72% of CKD patients had inadequate daily Vitamin K intake [16]. Among patients undergoing hemodialysis (HD), a 70%–90% prevalence of inadequate Vitamin K intake was reported, which was two-fold higher than those with normal renal function [17]. The low intake of Vitamin K could be attributed to dietary potassium restriction in CKD. Accordingly, increased daily intake of leafy green vegetables with low to moderate potassium (such as broccoli, cabbage, and kale) and potassium-reduced cooking strategies may be helpful in improving Vitamin K status.

Apart from dietary factors, the expression of Vitamin K epoxide reductase in the thoracic aorta was reduced in CKD status, evidenced by a rat model of adenine-induced CKD [18]. Moreover, UbiA prenyltransferase domain-containing protein-1 (UBIAD1), a Menaquinone-4 bioconversion enzyme, is decreasingly expressed in the kidney [18,19]. Recently, lipoproteins, which account for uptake and transportation of the fat-soluble Vitamin K, have been shown to be altered profoundly in experimental and human CKD [20].

The mechanisms link Vitamin K status and vascular calcification in chronic kidney disease

Among Vitamin K-dependent proteins, matrix Gla-protein (MGP) and osteocalcin mediate the close link between Vitamin K status and vascular calcification [5,6]. MGP is secreted from vascular smooth muscle cells and chondrocytes, whereas osteocalcin is secreted from osteoblast [5]. Uncarboxylated forms (inactive forms) of MGP and osteocalcin are carboxylated and activated through γ-glutamyl carboxylase, which converts specific glutamic acid residues into γ-carboxyglutamate. This carboxylation process is Vitamin K-dependent, in which reduced Vitamin K is oxidized to Vitamin K epoxide. The active forms of carboxylated MGP and osteocalcin then exert their effects by inhibiting vascular calcification and promoting bone formation, respectively [5,6]. Although the exact mechanisms remain unknown, the carboxylated MGP may inhibit vascular calcification by several potential mechanisms: (1) binding calcium ions or calcium crystals; (2) binding of bone morphogenetic protein-2, a growth factor transforming vascular smooth muscle cells into osteoblast-like cells; (3) anti-apoptosis of vascular smooth muscle cells; (4) binding to elastin, a potential substrate for calcification initiation [7,8]. Warfarin, a traditional anticoagulant, augments vascular calcification and retards bone formation by inhibiting Vitamin K epoxide reductase [Figure 1].

Accordingly, both uncarboxylated forms of MGP and osteocalcin are regarded as functional biomarkers for Vitamin K status, as well as surrogate markers for vascular calcification [21] and bone health [22].

Vitamin K and vascular health in chronic kidney disease: Evidence from observation studies

The close association between Vitamin K intake amount, as well as its functional biomarkers, and clinical outcomes was consistently reported in observational studies. Among 3401 nondialysis CKD participants retrieved from the NHANES III with extensive follow-up for a median of 13.3 years, high Vitamin K intake had lower hazard ratios (HRs) for overall mortality (HR = 0.85; 95% confidence interval [CI]: 0.72–1.00) and CV mortality (HR = 0.78; 95% CI 0.64-0.95), compared with low Vitamin K intake [16]. In the Chronic Renal Insufficiency Cohort, one of the largest CKD cohorts in the United States, low serum uncarboxylated MGP levels and high phylloquinone levels were associated with 21%–29% and 16%–19% decreased risk of all-cause mortality among 3066 nondialysis CKD patients, after a median 12.8 follow-up years [23]. Consistently, high serum uncarboxylated MGP levels were also reported to increase the mortality risk in patients with CKD stage 5 [24], diabetic CKD [25], ESRD undergoing peritoneal dialysis [26], and kidney transplant recipients [27].

A cohort study in 387 chronic HD patients disclosed the relationship between warfarin use, the severity of vascular
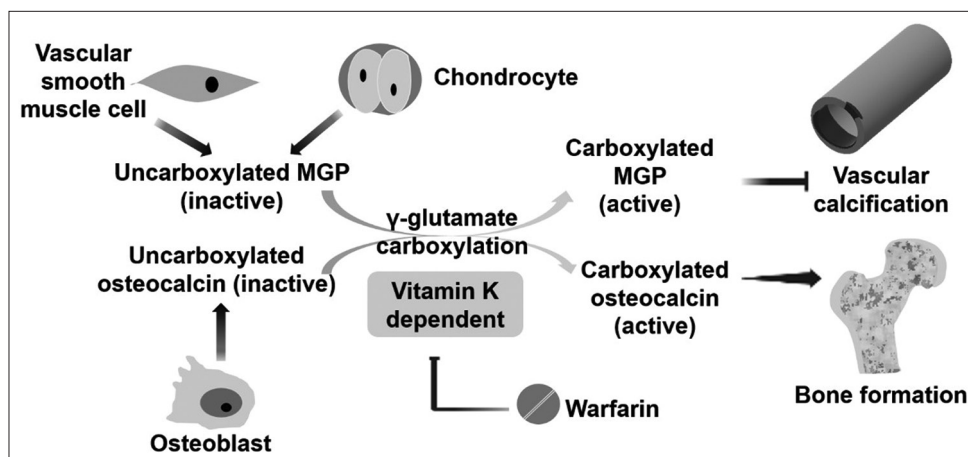
Figure 1: The role of Vitamin K status in the pathogenesis of vascular calcification. CKD, chronic kidney disease; ucMGP: Uncarboxylated MGP, RCT: Randomized control trial, ESRD: End-stage renal disease, HD: Hemodialysis; HR: Hazard ratio; CV: Cardiovascular

calcification, and mortality. Compared to those without warfarin use, patients on warfarin had a 2.6 and 2.9-folds increased odds ratios (ORs) for aortic calcification and iliac artery calcification, respectively and had a two-fold increased hazard risk of all-cause mortality (HR = 1.97, 95% CI: 1.02–3.84, $P = 0.046$) [28].

THE POTENTIAL BENEFIT OF VITAMIN K SUPPLEMENTATION: EVIDENCE FROM EXPERIMENTAL ANIMAL STUDIES

In a murine model, Scheiber *et al*. disclosed that 12-week high-dose Vitamin K_2 supplementation inhibited CV calcification in CKD rats fed with a high phosphate diet [29]. McCabe *et al*. showed that warfarin-treated CKD rats increased pulse pressure and pulse wave velocity and enhanced calcium content in the thoracic and abdominal aorta, renal artery, and carotid artery after a 7-week intervention; conversely, those treated with high-dose Vitamin K_1 inhibited the development of vascular calcification [30]. In another CKD rats model, warfarin treatment increased venous neo-intimal hyperplasia and calcification of arterialized veins, while Vitamin K_2 supplementation mitigated the detrimental effects of warfarin [31]. Similarly, Kaesler *et al*. reported that supplementation of 4-week Vitamin K_1 or K_2 in uremic rats reduced the tissue expression of uncarboxylated MGP in the aorta, which was associated with a decline in aortic and renal calcium content [32].

CLINICAL TRIALS INVESTIGATING THE EFFECTS OF VITAMIN K ON VASCULAR HEALTH IN CHRONIC KIDNEY DISEASE

Emerging clinical trials investigated the effects of Vitamin K supplementation on serum uncarboxylated MGP, vascular calcification, and clinical outcomes across the CKD spectrum. These results are described in the following section and summarized in Table 1.

A double-blind, randomized control trial to investigate the effect of 12-month daily 400 μg Vitamin K_2 supplementation on vascular stiffness among 159 CKD patients with stage 3b or 4 showed that, albeit a significant reduction in serum uncarboxylated MGP and osteocalcin levels in Vitamin K treatment group, there were no significant differences in pulse wave velocity as the primary outcome, as well as secondary outcomes, which included augmentation index, office blood pressure, N-terminal pro B-type natriuretic peptide, short physical performance battery, grip strength, and risks of falls [33]. In another small randomized, double-blind study, the effects of vascular calcification and atherosclerosis were compared between daily 10 μg cholecalciferol with 90 μg Vitamin K_2 and cholecalciferol alone among 42 nondialysis CKD patients with stage 3–5. After 270 days of supplementation, there is a significant decline in serum uncarboxylated MGP and osteocalcin levels in those with Vitamin K_2 supplementation. And, in cholecalciferol plus Vitamin K_2 group, the progression of common carotid intima-media thickness tended to be attenuated compared to those with cholecalciferol alone [34].

In 53 patients undergoing chronic HD, Westenfeld *et al*. observed a 4.5- and 8.4-folds increase in serum levels of uncarboxylated MGP and osteocalcin, compared with 50 normal healthy control subjects. The high levels of uncarboxylated MGP and osteocalcin in HD group declined after 6-week supplementation with daily 45, 135, or 360 μg Vitamin K_2 in a dose-dependent manner [35]. Similarly, a randomized control trial conducted by Caluwé *et al*. demonstrated that, among 200 patients undergoing chronic HD, 360, 720 or 1080 μg Vitamin K_2 supplementation thrice weekly lowered serum uncarboxylated MGP in a dose-dependent manner [36].

A 2-year randomized, double-blind trial (RenaKvit trial) compared the effect of pulse wave velocity and arterial calcification between daily 360 μg Vitamin K_2 and placebo among 48 dialysis patients [37]. Despite a significant reduction of uncarboxylated MGP in Vitamin K_2 group, the pulse wave velocity changes didn't differ between groups over the 2-year period. In addition, calcification of coronary arteries, aortic and mitral valves, and abdominal aorta progressed in both groups. Similarly, a significant decline in uncarboxylated MGP levels but not reduced aortic calcification in patients supplemented

Table 1: Summary of clinical trials of Vitamin K supplementation on vascular health in chronic kidney disease

Author, year	Study design	Participants	Treatment	Study duration	Serum ucMGP	Effects of Vitamin K — Vascular outcomes
					Nondialysis CKD	
Kurnatowska et al., 2015 [34]	Double-blind RCT	42 patients with stage 3-5	Cholecalciferol 10 μg + Vitamin K2 90 μg daily versus 10 μg cholecalciferol alone	9 months	Reduced in Vitamin D + K2 group	The progression of common carotid intima-media thickness attenuated in cholecalciferol + Vitamin K2 group
Witham et al., 2020 [33]	Double-blind RCT	159 patients with stage 3b or 4	Vitamin K2 400 μg daily versus placebo	12 months	Reduced	No significant differences in pulse wave velocity (primary outcome) and augmentation index, office blood pressure, N-terminal pro B-type natriuretic peptide, short physical performance battery, grip strength, and risks of falls (secondary outcomes)
					ESRD	
Westenfeld et al., 2012 [35]	RCT	53 chronic HD patients	Vitamin K2 45, 135, or 360 μg daily	6 weeks	A dose-dependent decline	—
Caluwé et al., 2014 [36]	RCT	200 chronic HD patients	Vitamin K2 360, 720 or 1080 μg thrice weekly	8 weeks	A dose-dependent decline	—
Oikonomaki et al., 2019 [38]	RCT	102 HD patients	Vitamin K2 200 μg daily versus control	12 months	Reduced	The changes in aortic calcification didn't differ between groups
Haroon et al., 2020 (Trevasc-HDK study) [41]	Open-label RCT	200 HD patients	Vitamin K2 360 μg thrice weekly versus control	18 months	Ongoing	
Levy-Schousboe et al., 2021 (RenaKvit) [37]	Double-blind RCT	48 dialysis patients	Vitamin K2 360 μg daily versus placebo	24 months	Reduced	The changes in pulse wave velocity, calcification of coronary arteries, aortic and mitral valves, and abdominal aorta didn't differ between groups
De Vriese et al., 2020 (Valkyrie) [39]	RCT	132 HD patients with atrial fibrillation	Warfarin versus rivaroxaban 10 mg daily versus rivaroxaban + Vitamin K2 group	18 months	Elevated in warfarin group, and reduced in rivaroxaban and rivaroxaban + Vitamin K2 group	There were no significant changes regarding pulse wave velocity, as well as calcification of coronary artery, thoracic aorta, and cardiac valve among the three treatment arms
De Vriese et al., 2021 (Valkyrie) [40]	RCT	132 HD patients with atrial fibrillation	rivaroxaban 10 mg daily + Vitamin K2 2000 μg trice weekly	36 months	—	The competing risk-adjusted HR for composite of fatal and nonfatal CV events was 0.41 (95% CI, 0.25–0.68) in rivaroxaban group and 0.34 (95% CI, 0.19–0.61) in rivaroxaban + Vitamin K2 group, compared with warfarin group
					Renal transplantation	
Mansour et al., 2017 [42]	Single-arm	60 renal transplant recipients	Vitamin K2 360 μg daily	8 weeks	Reduced	A 14.2% reduction in mean central pulse wave velocity was observed
Lees et al., 2021 (ViKTORIES) [43]	Double-blind RCT	90 renal transplant recipients	Menadiol diphosphate 5 mg trice weekly versus placebo	12 months	Reduced	The changes of vascular stiffness and calcification didn't differ between groups

CKD: Chronic kidney disease, ucMGP: Uncarboxylated matrix Gla-protein, RCT: Randomized control trial, ESRD: End-stage renal disease, HD: Hemodialysis, HR: Hazard ratio, CV: Cardiovascular, CI: Confidence interval

with 200 μg Vitamin K$_2$ daily among 102 HD patients was reported in another prospective randomized interventional study after 12-month follow-up period [38].

The Valkyrie study compared the effects of warfarin, 10 mg rivaroxaban daily, or 10 mg rivaroxaban daily plus 2000 μg Vitamin K$_2$ thrice weekly on vascular calcification and clinical outcomes among 132 HD patients with atrial fibrillation [39]. Compared to a significant elevation of uncarboxylated MGP levels in warfarin group, those in rivaroxaban and rivaroxaban plus Vitamin K$_2$ group displayed a decline in uncarboxylated MGP levels after 6 months. After an 18-month period of intervention, there were no significant changes regarding pulse wave velocity, as well as calcification of coronary artery, thoracic aorta, and cardiac valve among the three treatment arms. However, after extended follow-up for at least another 18 months, rivaroxaban and rivaroxaban plus Vitamin K$_2$ groups showed reduced HRs of a composite outcome of fatal CV disease, stroke, cardiac, and other vascular events, in comparison to the warfarin group [40].

Trevasc-HDK study, another randomized and open-label trial investigating the effects of 18-month oral Vitamin K$_2$ supplementation (360 μg thrice weekly) on vascular calcification in 200 HD patients, is ongoing [41].

In 60 renal transplant recipients, a single-arm clinical trial evaluating the effects of 8-week Vitamin K$_2$ supplementation (360 μg daily) on arterial stiffness showed a 55.1% reduction in mean uncarboxylated MGP and a 14.2% reduction in mean central PWV [42]. However, the ViKTORIES trial, a randomized, double-blind, placebo-controlled trial in 90 renal transplant recipients, failed to show any impact of 1-year supplemented 5-mg menadiol diphosphate trice weekly, a synthetic analogue of Vitamin K, on vascular stiffness and calcification [43].

INTERPRETATION OF CURRENT EVIDENCE

In summary, despite a decline in serum ucMGP levels, there is insufficient evidence to support the beneficial effects of Vitamin K supplementation on vascular calcification and stiffness in CKD and ESRD, as well as on CV events and mortality. Several possible reasons may be responsible for these findings. First, in patients with CKD, the pathogenesis of vascular calcification was multifactorial and was much more intricate than that in the general population. In this regard, a single strategy with Vitamin K supplementation may not be sufficient to reduce or mitigate the progression of vascular calcification. The combination of Vitamin K with other strategies aimed to exert synergic effects might be more effective. For example, through combination with Vitamin D, which promotes the production of Vitamin K-dependent protein, the randomized control trial conducted by Kurnatowska *et al.* reported the beneficial effects of Vitamin K$_2$ plus cholecalciferol on vascular stiffness in CKD stage 3–5 [34]. Second, considering the chronicity nature and high burden of vascular calcification among CKD patients, the study duration of most clinical trials may not be long enough to observe the clinical significance; further clinical trials with extended follow-up duration should be attempted to evaluate the long-term effects of Vitamin K. This chronicity pathophysiology of vascular calcification in CKD patients may also explain, at least in part, the discrepancies between clinical trials and experimental animal models, the latter of which showed promising benefit results of Vitamin K supplementation [18,29,32]. Notably, extended follow-up of Valkyrie study for additional 18 months disclosed a reduced risk of composited fatal and non-fatal CV events in rivaroxaban group and rivaroxaban plus Vitamin K$_2$ group, compared with warfarin group [40]. However, whether these results are attributed to the differences in Vitamin K status among groups or less safety profile of warfarin couldn't be clarified due to a lack of placebo group. Third, the optimal dose of Vitamin K to achieve the best efficacy for vascular health remains unknown. High-dose Vitamin K supplementation may enhance its biological effects theoretically but may also raise the concern of increased adverse effects. For example, MK-7 supplementation could influence anticoagulation sensitivity and attenuate drug effects in those on anticoagulants [44]. Otherwise, most aforementioned clinical trials with Vitamin K$_2$ doses ranging from 45 μg daily to 2000 μg trice weekly reported tolerable side effects without increased risks of thrombosis events. Fourth, whether the serum MGP levels, which reflect functional Vitamin K status, play a causal role in the pathogenesis of vascular calcification or are only a marker should be clarified further. In 188 HD patients, 6-week Vitamin K$_2$ supplementation resulted in a significant decline in serum ucMGP levels, but no increase in carboxylated MGP levels, the latter of which independently predicted vascular calcification, all-cause and CV mortality in that study [45]. Finally, the effects of Vitamin K supplementation may be hampered by uremic status, given the observation that the pharmacokinetics and biodistribution were prominently altered in advanced CKD and ESRD [20]. Since some clinical trials in non-CKD populations, including healthy elderly population [46], diabetic mellitus [47], and post-menopausal women [48], reported a benefit of Vitamin K supplementation on vascular health, whether Vitamin K supplementation in patients with earlier stages of CKD exhibited better efficacy should be determined in further studies.

CONCLUSION

Taken together, while the close relationships between Vitamin K deficiency and enhanced CV risks were reported in observational studies and the beneficial effects of Vitamin K supplementation on vascular health were suggested in animal studies, most clinical trials failed to show convincing CV benefits of Vitamin K. More clinical studies with large sample size and extensive follow-up periods are encouraged. Furthermore, clinical studies directed at identifying other forms of synthetic Vitamin K and their optimizing effective dose, determining suitable candidates who may benefit from Vitamin K supplementation, as well as combining multiple strategies are also urgently needed to expand our understanding regarding this important issue.

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