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The Role of Vitamin K in Vascular Calcification in Chronic Kidney Disease Patients

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Abstract:

Vascular calcification is closely associated with the increased cardiovascular mortality rate in chronic kidney disease (CKD) patients and has a high prevalence. However, current treatment options and outcomes are limited. Matrix γ-carboxyglutamic acid protein is a physiological inhibitor of vascular calcification, and its production requires the involvement of vitamin K for physiological activity. Supplementing vitamin K may be an effective treatment for preventing and managing vascular calcification in CKD patients, particularly in maintenance hemodialysis (MHD) patients who may have widespread vitamin K deficiency. This article provides a review of the role of vitamin K in vascular calcification in CKD patients.

Keywords:

Chronic kidney disease
Maintenance hemodialysis
Vitamin K
Matrix γ-carboxyglutamic acid protein
Vascular calcification

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1. Introduction

Cardiovascular disease is the leading cause of death in chronic kidney disease (CKD) patients, and vascular calcification is closely associated with the increased cardiovascular mortality rate and high prevalence in CKD patients. Among pre-dialysis CKD patients abroad, the prevalence of vascular calcification is as high as 79%, with severe vascular calcification present in 47% of patients [1]. In Chinese dialysis patients, the prevalence of calcification is as high as 77.3%.

Vascular calcification is not a passive deposition of minerals but an active and complex process similar to bone formation. In maintenance hemodialysis (MHD) patients, vascular calcification primarily includes intimal and medial calcification, with medial calcification being its main feature. Current research indicates that the core mechanism involves the transdifferentiation of vascular smooth muscle cells (VSMCs) from a contractile

phenotype to osteogenic and chondrogenic phenotypes.

Vitamin K deficiency is prevalent among MHD patients, and vitamin K supplementation may be an effective approach for preventing vascular calcification. However, existing research results on the role of vitamin K in vascular calcification in CKD patients remain inconsistent. This review summarizes the current findings.

2. Vitamin K-dependent protein: Matrix γ-carboxyglutamic acid protein

Vitamin K is an essential fat-soluble vitamin for the human body, with its primary biological role as a necessary cofactor for the carboxylation of vitamin K-dependent proteins. All vitamin K-dependent proteins contain glutamine residues that are converted into γ-carboxyglutamic acid domains with high affinity for calcium ions.

Matrix γ-carboxyglutamic acid protein (MGP) is a secretory vitamin K-dependent protein found in the extracellular matrix. It is primarily synthesized by chondrocytes in cartilage and by smooth muscle cells and endothelial cells in the arterial vessel wall. In the vascular media, MGP is almost exclusively expressed by smooth muscle cells, while in the intima, it is expressed mainly by smooth muscle cells, macrophages, and endothelial cells.

MGP was initially isolated from bone tissue and was considered a vitamin K-dependent protein involved in bone metabolism. Later research revealed that the MGP gene and its expression products are closely associated with various diseases, such as osteoporosis, ectopic calcification, and cardiovascular diseases.

Early studies showed that mice with MGP gene knockout died approximately two months after birth due to vascular rupture and heart failure. Autopsies revealed extensive calcification of the aortic valve, elastic arteries, and muscular medium and large arteries. Subsequently, research by El-Maadawy *et al.* also confirmed vascular calcification in MGP-deficient mice, with cartilage formation commonly observed in calcified arteries [2].

In a prospective study, the serum expression of MGP in postmenopausal women with coronary artery calcification was measured, revealing a significant negative correlation between the severity of coronary calcification and MGP expression [3].

3. dp-ucMGP levels and vascular calcification

The activation of MGP requires two post-translational modifications: phosphorylation of cysteine residues and carboxylation of glutamic acid residues. These modifications are often incomplete, resulting in the presence of four different types of MGP in circulation: dephosphorylated uncarboxylated MGP (dp-ucMGP), dephosphorylated carboxylated MGP (dp-cMGP), phosphorylated uncarboxylated MGP (p-ucMGP), and phosphorylated carboxylated MGP (p-cMGP).

Vitamin K is an essential cofactor for γ-glutamyl carboxylase, the rate-limiting enzyme in MGP carboxylation. A deficiency of vitamin K in the vascular system triggers a negative feedback mechanism, leading to an increase in inactive uncarboxylated MGP. Among the MGP forms, only dp-ucMGP lacks a high affinity for precipitated calcium salts and hydroxyapatite, which prevents its free circulation in the bloodstream. Hence, monitoring dp-ucMGP levels in circulation has become a promising biomarker for studying cardiovascular endpoints and assessing the vitamin K status of the vascular system.

Circulating dp-ucMGP levels reflect changes in vascular vitamin K status. Vitamin K supplementation reduces dp-ucMGP levels, whereas vitamin K antagonists increase them. In the general population, circulating dp-ucMGP levels range between 400 and 500 pmol/L [4]. The concentration of dp-ucMGP depends not only on the vitamin K status of the body but also on the total MGP levels, which increase with age and cardiovascular disease.

A prospective cohort study of 571 women with an average age of 57.3 years revealed that plasma dp-ucMGP levels were significantly correlated with coronary artery calcification scores [5]. Research by Aoun M et al. showed that circulating dp-ucMGP levels in MHD (maintenance hemodialysis) patients were linearly related to aortic calcification scores, suggesting dp-ucMGP as a potential marker of vascular calcification [6].

A cross-sectional study involving 198 type 2 diabetes patients with normal or mildly impaired renal

function found that circulating dp-ucMGP levels were independently associated with arterial calcification scores [7]. Another study of 107 CKD stage 2–5 patients indicated that plasma dp-ucMGP levels increased as the glomerular filtration rate declined and were positively correlated with aortic calcification scores [8]. A similar cross-sectional study of 83 CKD stage 3–5 patients also found that dp-ucMGP levels increased with the severity of renal impairment and positively correlated with abdominal aortic calcification severity [9].

Additionally, cohort studies have shown that plasma dp-ucMGP levels were significantly elevated in MHD patients and were strongly associated with arterial calcification scores [10]. However, some studies have reported conflicting results, arguing that dp-ucMGP levels in MHD patients only reflect vitamin K deficiency in the vascular system and are not associated with vascular calcification, making them unsuitable as surrogate markers for vascular calcification, such as coronary artery calcification scores and arterial stiffness [11].

While the relationship between dp-ucMGP levels and arterial calcification remains controversial, elevated dp-ucMGP levels are associated with a significantly increased risk of all-cause or cardiovascular mortality in CKD patients. All-cause mortality increases 1.5-fold in CKD stage 2–5 patients [8] and nearly threefold in MHD patients [11].

Supplementation with MK-7 (a form of vitamin K2) can reduce dp-ucMGP levels. However, even the highest doses of MK-7 cannot normalize dp-ucMGP levels, possibly due to increased MGP synthesis caused by underlying CKD. This makes interpreting dp-ucMGP levels as a marker of vitamin K status more complex in MHD patients. Mendoza *et al.* found that calcium and PTH stimulation increased MGP synthesis [12]. Some researchers attribute this to decreased γ-glutamyl carboxylase activity in MHD patients. Even before obvious calcification occurs, reduced γ-glutamyl carboxylase activity has been observed in multiple tissues of uremic patients, potentially contributing to vascular calcification and functional vitamin K deficiency in MHD patients.

Vitamin K supplementation can partially reduce extraosseous calcium deposition and increase γ-glutamyl carboxylase activity [13]. This suggests that vitamin K supplementation may not only improve low vitamin K intake but also restore endogenous vitamin K circulation. MHD patients may require higher doses or prolonged supplementation to achieve effective results.

4. Effects of vitamin K on vascular calcification

In ESRD patients with atrial fibrillation, vitamin K antagonists such as warfarin are commonly used to prevent thrombosis. This creates a clinical model of functional vitamin K deficiency, which may promote the formation and progression of vascular calcification. Early studies found that HD patients on long-term warfarin therapy had more severe aortic valve calcification [14]. Subsequent research demonstrated worsening calcification in the aorta and iliac arteries, which was significantly associated with decreased ucMGP levels [10]. More recent studies have shown that coronary artery calcification is also more severe in these patients [15,16]. Data from the German Calciphylaxis Registry identified warfarin therapy as a risk factor for calciphylaxis [17]. A study in Japan reported that warfarin use in MHD patients increased the risk of calciphylaxis by tenfold [18].

In the Rotterdam Study, over 4,800 healthy individuals were supplemented with 45 μg of vitamin K2 daily for 10 years. Results showed a 50% reduction in vascular calcification incidence and cardiovascular mortality, and a 25% reduction in overall mortality [19]. Vitamin K1 did not exhibit similar effects, though some studies suggest that vitamin K1 may delay aortic valve calcification [20].

The mechanisms underlying vascular calcification in CKD patients are more complex and influenced by various factors. Epidemiological surveys indicate that 90% of dialysis patients exhibit vitamin K deficiency [21]. In uremic mice, vitamin K supplementation significantly reduced calcium deposition in the kidneys, with a parallel reduction in aortic calcium deposition. In the heart and kidneys, doses of vitamin K lower than 2,500 mg/kg were as effective in preventing calcification. However, after vitamin K1 supplementation, increased vitamin K2 concentrations were not detected in the liver or kidneys, suggesting that the observed effects might be due to vitamin K1 itself or its conversion to vitamin K2 in the

aorta.

While MK-7 supplementation in MHD patients can reduce dp-ucMGP levels, its effects on vascular calcification remain inconclusive. A recent randomized, double-blind, controlled study included 35 diabetic patients with a glomerular filtration rate (GFR) > 30 mL/min. After six months of daily MK-7 supplementation at 360 μg, there was no significant reduction in arterial calcification scores compared to placebo, indicating that MK-7 did not inhibit vascular calcification [22].

The KING study evaluated post-kidney transplant patients who received 360 μg of vitamin K2 daily. Results showed that vitamin K2 significantly slowed the progression of arterial stiffness, as indicated by reduced pulse wave velocity (PWV), but no clear evidence suggested that vitamin K2 inhibited vascular calcification [23]. A one-year randomized controlled study by Oikonomaki *et al.* found no definitive effect of MK-7 on delaying aortic calcification [24].

Similarly, a randomized controlled trial by De Vriese *et al.* included 132 MHD patients with atrial fibrillation. Participants were divided into two groups: one received warfarin, and the other received rivaroxaban plus vitamin K2. After 18 months, although dp-ucMGP levels significantly decreased in the vitamin K2 group, there were no significant differences in PWV, thoracic aortic calcification scores, coronary artery calcification scores, or heart valve calcification scores between the two groups, indicating that vitamin K2 did not delay vascular calcification [25].

In another study, Kurnatowska *et al.* randomized 43 non-diabetic CKD stage 3–5 patients into two groups: one supplemented with vitamin K2 + D and the other with vitamin D alone. After one year, the common carotid intima-media thickness (CCA-IMT) was significantly lower in the vitamin K2 + D group compared to the vitamin D group. Both groups experienced an increase in coronary artery calcification scores (CACS), though the increase was slightly slower in the vitamin K2 + D group, without statistical significance [26]. This suggests that vitamin K2 may delay atherosclerosis progression, as low-carboxylated MGP is abundant in atherosclerotic plaques, and vitamin K supplementation enhances MGP carboxylation [8]. However, no significant effect of vitamin K2 on coronary artery calcification was observed. Further analysis revealed that in patients with low baseline CACS, vitamin K2 markedly slowed the progression of CACS, suggesting that early use of vitamin K2 might delay arterial calcification. In contrast, it may be ineffective for severe arterial calcification, which is difficult to prevent or treat.

Recent observational studies indicate that a high dietary intake of vitamin K2 in non-dialysis CKD patients is associated with reduced risks of coronary artery disease and vascular calcification [27]. However, the effects of vitamin K supplementation on vascular calcification in CKD patients remain inconclusive. Several cohort studies are ongoing worldwide.

5. Adverse reactions of vitamin K

The safety of vitamin K supplementation has also been a subject of concern among researchers. Theoretically, excessive vitamin K intake could promote coagulation. Therefore, whether long-term vitamin K supplementation, especially in elderly and MHD patients, might have adverse effects, such as an increased risk of thrombotic events, has been a major focus of scholarly attention. However, the number of glutamine residues available for carboxylation in the vitamin K-dependent coagulation factor carboxylation reaction is limited. Thus, excessive vitamin K does not lead to further carboxylation of other residues. Low-dose MK-7 supplementation has been shown to improve the extrahepatic vitamin K status, but thrombin generation in healthy subjects was not affected [28].

Furthermore, vitamin K-dependent anticoagulant proteins operate in parallel with coagulation factor activation, maintaining the balance of coagulation in the body. A long-term, large-sample observational study found that vitamin K intake is not a risk factor for stroke. Long-term vitamin K supplementation was not associated with an increased risk of thrombosis or other adverse effects [22,24].

Currently, evidence confirms that CKD patients, particularly MHD patients, exhibit vitamin K deficiency, with significantly elevated levels of inactive vascular calcification inhibitors such as MGP. Vitamin K supplementation has been shown to reduce dp-ucMGP levels. However, the effects of vitamin K supplementation on vascular calcification remain controversial.

Additionally, determining the extent of vitamin K deficiency in MHD patients, and subsequently tailoring individualized and precise supplementation regimens to prevent or delay vascular calcification, as well as to reduce the incidence of cardiovascular disease and mortality, requires further clarification through large-scale, multicenter studies.

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