Original Article

Cardiovascular Health And Vitamin K Status: Evidence From Observational And Clinical Studie

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Abstract

Vitamin K is a fat-soluble vitamin required for the activation of several vitamin K-dependent proteins to confer functioning. A increasing amount of research shows that vitamin K is good for bones and cardiovascular health. This review provides an overview of the most important research on the relationship between circulating vitamin K levels and cardiovascular outcomes. An essential matrix gla protein (MGP)-dependent inhibitor of vascular calcification. Vascular calcification and high amounts of uncarboxylated, dephosphorylated MGP have been linked, and vitamin K therapy can help. In this systematic review, we present the evidence that vitamin K supplementation improves surrogate markers of cardiovascular disease, such as calcification of the arteries and valves, atherosclerosis, and arterial stiffening. By searching Ovid MEDLINE, Embase, the Cochrane Central Registry of Controlled Trials, and the Web of Science Core Collection, researchers were able to find information from adult-specific controlled trials. Among nine randomised controlled trials, including trials of vitamin K1 or K2 supplementation, that evaluated a proxy for cardiovascular disease, such as arterial calcification, atherosclerosis, or arterial stiffening, we found nine studies that were suitable for review.

Keywords: Vitamin K Supplementation, cardiovascular disease; vascular calcification; arterial stiffness; atherosclerosis; matrix Gla protein.

1. INTRODUCTION

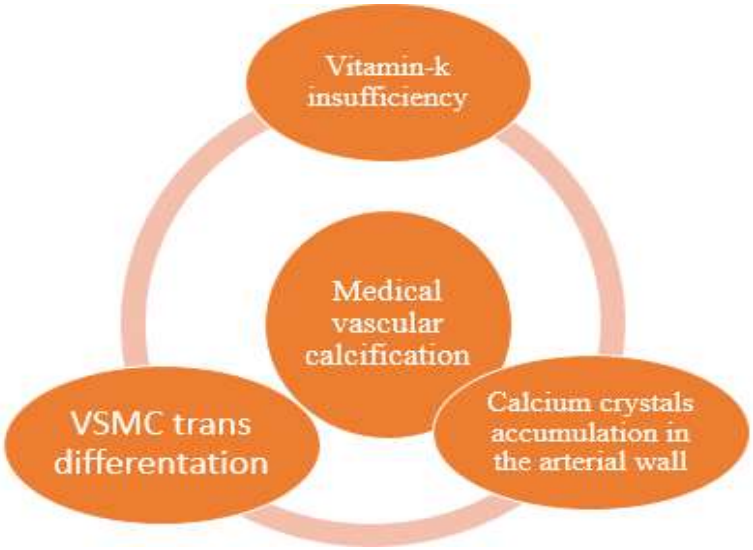
The greatest cause of illness and mortality worldwide is cardiovascular disease (CVD). In the ageing population, calcification of arteries and valves raises the risk of CVD and death. Calcification is a common complication of diabetes mellitus and chronic kidney disease (CKD), and it is a standalone risk factor for cardiovascular mortality [1]. Despite the fact that these groups frequently have hypertension and dyslipidemia, these classic cardiac risk factors can not entirely explain the higher risk.

A fat-soluble vitamin, vitamin K is primarily recognised for its role in blood clotting. Henrick Dam made the discovery of vitamin K in 1939. He named the chemical vitamin K after the Danish word for blood clotting, koagulation[1,4].

Humans eat two forms of vitamin K: vitamin K1 (phylloquinone), which is mostly present in green leafy vegetables, and vitamin K2 (menaquinones), which is mostly present in animal products, fermented dairy goods like cheese, and natto (fermented soy beans). The variety of vitamin K forms present in vitamin K2 differs from those present in vitamin K1 in terms of side-chain length and degree of saturation. Vitamin K2, which is the most physiologically active version of the vitamin, has a longer half-life than vitamin K1 (days vs. hours). Matrix Gla protein (MGP) is a vitamin K-dependent protein (VKDP) that counteracts vascular mineralization. MGP is highly expressed in calcifying arteries where it is thought to inhibit extra-osseous calcification by binding to growing hydroxyapatite crystals and inhibiting BMP-2 [2].

In order to be activated, vitamin K-dependent ϒ-carboxylation of the Gla residues is required. In addition to carboxylation, MGP is also phosphorylated post-translationally. In the setting of vitamin K deficiency or antagonism, the post-translational carboxylation of vitamin K-dependent proteins is impaired, resulting in increasing inactive fractions of these proteins in circulation [3]. Vitamin K deficiency is common in CKD [4] and ESKD [5], particularly in those on vitamin K antagonist medications such as warfarin [3]. Further, observational studies have suggested an association between dietary intake of vitamin K as well as biomarkers of vitamin K and reduced arterial calcification [6,7,8,9]. Thus, there is rationale to suggest that correcting vitamin K deficiency by supplementation with different forms of vitamin K may decrease calcification and improve CVD outcomes. We performed a systematic review of clinical trials that examined

whether vitamin K supplementation influences surrogate measures of cardiovascular disease such as vascular calcification, vascular stiffness and intimal media thickness.



Vitamin-K status and vascular calcification: Evidence from Observational and Clinical Studies

2. MATERIALS AND METHODS

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, this systematic review was carried out [10]. The following was the review question, which was created using PICOS (Population, Intervention, Comparison, Outcomes, and Settings) criteria (Table 1): Does supplementing with vitamin K affect proxies for cardiovascular disease in randomised trials?

Table 1. PICOS (Population, Intervention, Comparison, Outcomes and Settings) criteria for the inclusion of studies evaluating the effects of vitamin K supplementation on vascular properties.

Parameter	Inclusion Criteria
Population	Adult
Intervention	Controlled Vitamin K (K1 or K2) intake
Comparison	Non-exposed control group
Outcome	Any measurement of vascular calcification, vascular stiffness, vascular flow limitations (e.g., intimal media thickness, pulse wave velocity)
Setting	Randomized controlled trials

2.1. Eligibility Criteria

The following inclusion criteria were applied to obtain the selected studies: parallel randomized controlled trials of adult participants of any ethnicity that involved vitamin K supplementation with a control group (placebo or no-treatment control group) for a period of >12 weeks and measured a surrogate outcome related to cardiovascular disease at baseline and study end. Trials published up until April, 2020 were considered

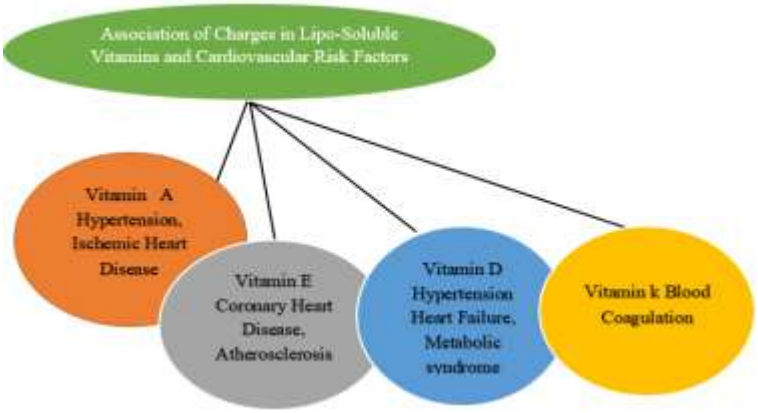
2.2 Circulating Vitamin K Status Markers

Circulating nutrient biomarkers are considered more objective measures of nutrient status compared to dietary intake measures and reflect both intake and metabolism. Multiple biomarkers are available to measure vitamin K status, but none of them is robust enough to be considered “gold standard” [12]. Circulating vitamin K1 concentrations decrease during vitamin K1 depletion and increase with vitamin K1 supplementation [13]. An important limitation of the measurement of plasma vitamin K1 is that it mainly reflects the intake of the previous days due to its relatively short half-life time of 1–3 h [14].

2.3. Search Methods for Identification of Studies

A three-step search strategy was utilized to locate published studies for this review. An initial limited search of Ovid MEDLINE was executed, followed by an analysis of eligible studies to identify relevant text words contained in the title, abstract and author provided keywords, and the subject headings assigned to the article. A second search using all relevant text words and subject headings was then executed in Ovid MEDLINE and subsequently adapted for the other databases (Appendix A). The following databases were searched from inception in April 2020: Ovid MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Web of Science Core Collection. No language or date restrictions were applied. The total number of records from all databases was 7668. After removing duplicate references in Covidence systematic review software, the total number of records screened was 5255. Bibliographies of included studies were reviewed for further references to relevant trials and abstracts from the last 5 years of the American Society of Nephrology Kidney Week and the annual meeting of the European Renal Association-European Dialysis and Transplant Association were hand-searched.

Effectiveness of some Vitamins in the Prevention of Cardiovascular Disease



3. CARDIOVASCULAR-RELATED OUTCOMES

No matter where it occurs anatomically, vascular calcification is a major risk factor for cardiovascular death [18]. Arterial stiffening, higher systolic pressure, and increased cardiac workload are all caused by calcification in the vasculature [19]. Vascular calcification does not yet have an effective treatment; instead, efforts are focused on symptom relief. Thus, it is critical to comprehend the fundamental mechanisms governing these processes if we are to reduce the burden of vascular calcification and related health-care expenses.

A substantial body of research using animal models in experiments shows that vitamin K contributes to vascular calcification by carboxylating MGP [2, 20]. An MGP knock-out model had significant coronary artery calcification that caused aortic rupture and early mortality [2]. Further, vitamin K antagonism due to warfarin antagonizes vitamin K-dependent carboxylation of MGP leading to rapid arterial calcification [21]. In addition, a high vitamin K diet is able to reverse aortic calcification after warfarin treatment in rats [22].

The relationship between circulating vitamin K status biomarkers with cardiovascular-related outcomes received growing research interest in the last 5 years. We examined human evidence of circulating vitamin K status and cardiovascular health, with a particular focus on chronic kidney disease (CKD) patients, a group characterized with a disproportional high risk for vascular calcification and CVD death[13].

3.1. Biological Role of Vitamin K

For VKDPs to function properly, vitamin K is required. The cofactors VK1 and VK2 help the enzyme -glutamyl carboxylase function. The carboxylation of proteins, which is dependent on vitamin K, is catalysed by this enzyme by attaching carboxyl groups to Glu residues. Many blood clotting proteins (proteins C, S, M, Z, factors VII, IX, X, and prothrombin), Gas6 (Growth Arrest-Specific 6 Protein), bone (BGP or osteocalcin OC), matrix (MGP), periostin, and GRP are among the proteins that make up this group, which has at least 18 proteins (Gla Rich Protein). Prothrombin, MGP, and OC are the three VKDPs that are most crucial. These proteins play critical roles in the formation of clots, defence against vascular calcification (VC), and mineralization of bone. Gas 6 weighs 75 kDa, making it one of the biggest VKDPs. n healthy people, its plasma concentrations range from 2.5 to 18.8 g/L. After vitamin K carboxylation, this protein has an N-terminal Gla domain and is significantly similar to protein S. Gas is thought to be the endogenous ligand for the TAM and is abundantly present in the heart, brain, kidney, lung, and other tissues with the exception of the liver. Tyro3, Axl, and Mer are the three receptors that make up the acronym TAM. The receptor with the highest affinity for Gas 6 is Axl. The interaction between Gas 6 and the TAM receptor depends mostly on the vitamin K-dependent carboxylation. **Figure 1.** illustrates the cycle and functions of vitamin K.

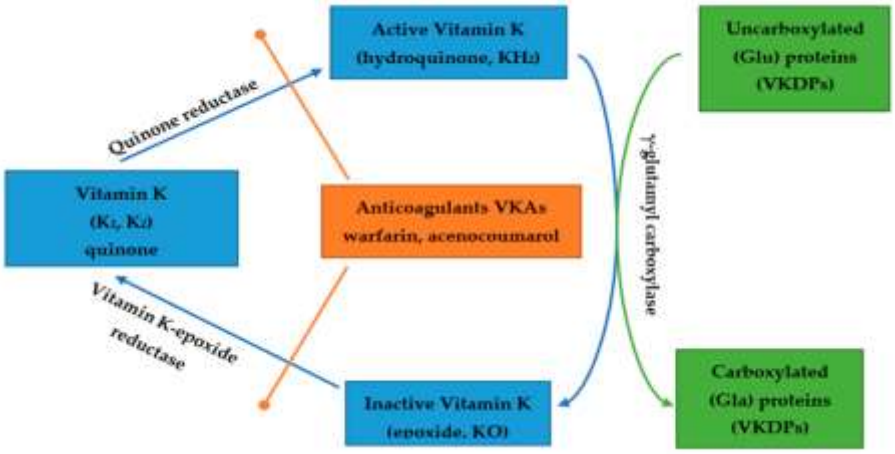


Figure 1. The vitamin K cycle and action. VKAs—vitamin K antagonists, VKDPs—vitamin K-dependent proteins, Glu-glutamate, Gla-γ-carboxyglutamate, KH2-vitamin K hydroquinone, KO-vitamin K epoxide.

3.2. Circulating Vitamin K and CVD-Related Outcomes

A rising number of research evaluated the cross-sectional connection between the level of circulating vitamin K and outcomes associated to CVD [17]. Higher plasma dp-ucMGP and poor echocardiographic parameters were observed to be correlated univariately in two Norwegian studies, although multivariable statistical analyses were not performed in either study. Higher plasma dp-ucMGP concentrations were associated with a trend towards a higher coronary artery calcification (CAC) score of 0.091 (95% confidence range, 0.01, 0.19) among post-menopausal women, according to a study by Dalmeijer et al. [23]. Higher dp-ucMGP was substantially related with a greater odds of peripheral arterial calcification score, according to Liabeuf et al. : odds ratio 1.88 (1.14, 3.11) [24]. In populations from various nations, higher carotid-femoral pulse wave velocity (cf-PWV) was consistently linked to higher plasma dp-ucMGP. In the MESA study, no association between circulating DCP and cardiovascular calcification was observed in healthy participants
So far, vitamin K intervention trials with hard clinical endpoints are missing. One intervention trial studied the effect of vitamin K vs. placebo on arterial stiffness in healthy post-menopausal women . After 3 years, the beta stiffness index as a measure of mechanical arterial properties decreased significantly in the menquinone-7 group compared to that of the placebo. More studies are clearly needed to investigate whether vitamin K supplementation improves cardiovascular health.

In a multi-ethnic cohort study, higher circulating DCP was associated with a higher risk of ischemic CVD in a population enriched for ankle-brachial pressure ≥1.4 [16]. In a Flemish population study, Mendelian randomization was applied using genetic variation associated with dp-ucMGP concentrations[18,19].

3.3. Chronic Kidney Disease Populations

Vascular calcification is quite common in people with CKD and is a reliable indicator of cardiovascular death. Furthermore very common in CKD people is vitamin K insufficiency. Vitamin K is essential for vascular calcification susceptibility in experimental CKD models. The use of low dosages of vitamin K1 or the therapeutic administration of vitamin K antagonists both significantly exacerbated the degree of vascular calcification in CKD-affected mice. Moreover, high vitamin K doses during treatment boost vitamin K tissue concentrations, slow down the development of calcification, and restore tissue calcium content to levels comparable to those of non-CKD animals[20.23].

4. INTERACTION WITH VITAMIN D

Although it can be obtained by eating foods like fatty fish, dairy products, and eggs, vitamin D is mostly produced by the skin when exposed to sunshine. It is a fat-soluble vitamin. For maximum biological activity, vitamin D is converted by the kidney into its most active form, 1,25-dihydroxyvitamin D, also referred to as calcitriol. Although vitamin K's involvement in cardiovascular health has primarily been researched in isolation, new information points to a synergistic relationship between vitamin K and vitamin D. Our current knowledge of the biochemical function of vitamin K cannot account for these data, but they do show that vitamin D may have an impact on MGP concentrations[14,16].

Some animal studies indicate that calcitriol has direct effects on the γ-carboxylase system by stimulating vitamin K-dependent proteins , which means that the amount of vitamin K-dependent proteins available for carboxylation is vitamin D dependent. This may lead to higher circulating levels of under-carboxylated MGP and calcium deposition in the vasculature, which could further increase the risk of vascular calcification and CVD. In vitro studies also support the concept of a synergistic effect of vitamin K and vitamin D. These studies found that the matrix gla protein gene promoter contains a vitamin D response element, capable of a two- to threefold enhanced matrix gla protein expression after vitamin D binding . The effect of vitamin D combined with vitamin K on dp-ucMGP is therefore expected to be larger than that of solely vitamin K; however, this should be further explored[18,19].

4.1 Clinical Trials with Combined Vitamin D and K Supplementation

Two human intervention studies have so far looked at how vitamins D and K together affect vascular function and calcification in healthy populations. The vitamin D + K group in post-menopausal women-maintained vessel wall features of the carotid artery over a 3-year period of follow-up, while the control group and the vitamin D-only group drastically deteriorated. To ascertain what transpires after supplementation, vitamin K status was not evaluated as a metric of compliance. Also, in a 3-year, double-blind, randomised controlled trial of older men and women free of clinical CVD, daily supplemental vitamin K was given at amounts that could be obtained by eating a lot of green, leafy vegetables (500 g/day) along with 600 mg. Calcium carbonate and 10 μg (400 IU) vitamin D did not result in lower CAC progression compared to the calcium + vitamin D group. In a subgroup analysis of participants who were ≥85% adherent to supplementation, there was less CAC progression in the vitamin K + calcium and vitamin D group than in the calcium and vitamin D group alone. These data are hypothesis generating, and further studies are warranted to clarify the mechanism[12,17].

Recommendation for Future Research

- Study the effect of different vitamin K forms in relation to cardiovascular-related outcomes.
- Define the clinical cutoff value for various vitamin K status markers and define vitamin K deficiency.

• Deepen the knowledge on the interaction between vitamins D and K and cardiovascular-related outcomes.

CONCLUSIONS

Overall, observational studies show that vitamin K has a potential function in cardiovascular health, especially in high-risk and chronic kidney disease groups. Few vitamin K intervention trials have been conducted with non-clinical cardiovascular outcomes. In contrast to vitamin K supplementation, the majority of clinical research looked at vitamin D + K supplementation, which may have synergistic effects. Vitamin D may maintain the action of proteins that are dependent on vitamin K, improving vascular health. It would be helpful to determine whether vitamin K is causally connected to vascular calcification and CVD by assessing vitamin K status using a variety of biomarkers in prospective studies and well-designed randomised trials.

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