International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

REVIEW ARTICLE

The Effects of Vitamin K Supplementation in Vascular Calcification: A Systematic Review

Maryam Sharafi Miab[1], Seyed Jalil Masoumi[2,3,4*], Neda Haghighat[3], Morteza Zare[3]

1. Student Research Committee, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
2. Nutrition and Food Sciences Research Center, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
3. Nutrition Research Center, Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
4. SUMS Employees Health Cohort Study, Shiraz University of Medical Sciences, Shiraz, Iran

ARTICLE INFO

Keywords:
Vitamin K
Matrix Gla Protein (MGP)
Coronary Artery Calcification (CAC)
Pulse Wave Velocity (PWV)

**Corresponding author:*
Seyed Jalil Masoumi,
Assistant Professor of Nutrition Research Center, Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran.
Tel: +98-71-32300050
Email: masoumi7415@gmail.com
Received: January 29, 2018
Revised: February 17, 2019
Accepted: February 26, 2019

ABSTRACT

Background: Vascular calcification is a predictor of cardiovascular morbidity and mortality, which can be evaluated by pulse wave velocity (PWV) and Coronary Artery Calcification score (CAC. s). Vitamin K-dependent matrix Gla protein (MGP) is an important inhibitor of calcification. The aim of this systematic review was to assess the effect of high-dose vitamin k supplementation on vascular calcification.

Methods: In this systematic review, a literature search in PubMed was undertaken with using the keywords "vitamin k1 supplementation" OR "phylomenadion supplementation" OR "vitamin k2 supplementation" OR "menaquinone supplementation" OR "vitamin k3 supplementation" OR "menadion supplementation" and "calcification", and then qualified articles were used.

Results: Vitamin K1 supplement was not associated with dephosphorylated-uncarboxylated MGP (dp-uc MGP) level and PWV level. However, it was associated with less CAC progression. Vitim K2 supplement was correlated inversely with dp-uc MGP level and decrease in PWV but no difference CAC progression.

Conclusion: Based on results that was obtained from this systematic review, we expressed conclusively that taking vitamin K supplements especially vitamin K2 can decrease inactive MGP levels and slow the progression of CAC in healthy older adults with pre-existing CAC and improve arterial stiffness.

Please cite this article as: Sharafi Miab M, Masoumi SJ, Haghighat N, Zare M. The Effects of Vitamin K Supplementation in Vascular Calcification: A Systematic Review. Int J Nutr Sci. 2019;4(2):54-58.

Introduction

Older patients, and those with diabetes and chronic kidney disease (CKD), are at substantially increased risk of cardiovascular disease (CVD). Independence of traditional cardiovascular risk factors, increased vascular stiffness (VS) is associated with future cardiovascular events (1) and often associated with presence of vascular calcification (VC) (2). Calcification is a slowly progressive process and caused by an imbalance between the mechanisms that promote and inhibit the deposition of calcium in the vascular wall (3). Because of imbalance between procalcific and calcification inhibiting substances leading to osteogenesis (4). Various procalcifying factors, such as calcium and phosphate, are antagonized by a network of regulatory proteins in vascular tissue (5). Irrespective of the histoanatomic and etiological characteristics of vascular calcifications, decreased activity of endogenous calcification inhibitors,

such as the potent matrix Gla protein (MGP) (6-9), enables mineralization of the vascular wall. MGP is a small, approximately 10-kDa protein that is expressed primarily by osteoclasts, chondrocytes, and vascular smooth muscle cells. Its activation confers the calcification inhibitory activity and depends on two posttranslational processes. Active MGP (phosphorylated and carboxylated) inhibits local crystal growth and vascular smooth muscle cell apoptosis, while dephosphorylated-uncarboxylated MGP (dp-ucMGP) is inactive, has low affinity for calcium, and is then released in the circulation (4, 10).

It was demonstrated that plasma levels of dp-uc MGP are markers of vascular vitamin K status with high levels indicating vascular vitamin K deficiency and are positively associated with arterial stiffness (11). Vitamin K is required for the function of MGP through its role as an enzyme cofactor in the γ-carboxylation of the protein (12). Pulse Wave Velocity (PWV) and Coronary Artery Calcification score (CAC score) are two important vascular calcification indicators which are decreased by vitamin K supplementation. Arterial stiffness was evaluated by measurement of PWV. PWV is a non-invasive, reproducible technique that has previously been used as a surrogate of CVD in the kidney transplant population and is considered the gold standard to directly measure arterial stiffness. A detailed description of the PWV technique has previously been described (13), which may be performed on various arteries including carotid, femoral, brachial. aim CAC score is an established quantitative tool for assessing subclinical atherosclerosis (14).

The group of vitamin K vitamins comprises phylloquinone (vitamin K1) and several menaquinones (vitamin K2). Phylloquinone is found in green leafy vegetables, whereas the main dietary source of menaquinones is fermented food such as cheese (15). The phylloquinone (vitamin K1), as this is essential in the activation of several coagulation factors, but menaquinone (MK) is another very important vitamin K species. MK is deemed necessary for γ-carboxylation of proteins involved in the inhibition of arterial calcification (3). In this review, our aim was to discuss the therapeutic effects of supplementation of vitamin K on artery calcification among renal transplant patients and haemodialysis patient and in patient with CAC was postulated to be associated with reduction in dp-uc MGP and subsequent improvement in arterial stiffness.

Materials and Methods

Search Strategy

For the systematic review, we searched for articles investigating the effects of vitamin K supplementation on vascular calcification in PubMed database up to November 1st 2018. A group of search terms were used including "vitamin k1 supplementation" OR "phylomenadion supplementation" OR "vitamin k2 supplementation" OR "menaquinone supplementation" OR "vitamin k3 supplementation" OR "menadion supplementation" and ''vascular'', ''vessel'', ''artery'', ''arterial'', ''stiffness'', and "calcification".

Study Selection

The studies were selected, if they had the following inclusion criteria were present like randomized controlled design; and reporting the effects of vitamin k supplementation in vascular calcification. Exclusion criteria were adult patients with CAC or hemodialysis patient and trials with oral vitamin K supplementation and assessing the CAC measurement and biochemical measurement and measurement of PWV. Finally, six articles were included in the systematic review (Figure 1).

Data Extraction

The first author's name, publication year, participants, characteristics, duration, dose of vitamin K interventions and outcome measures were enrolled.

Results

We found 129 articles in the initial search, 108 of which were excluded, due to their irrelevant titles and nine studies were excluded by reading the abstracts; six of them were removed due to study of the full texts. Then, six articles were included in this systematic review, shown in Table 1. Trials with specified criteria to assess the improvement of vascular calcification with one or more outcomes such as CAC-score, PWV, circulating dp-uc MGP, were included in this review.

CAC-Score Measurement

CAC-score was reported in two studies. One of them reported those in the phylloquinone treatment group had less progression of CAC than did those in the control group (P=0.03) (12) and one study reported CAC that significantly increased despite the MK4 treatment (16).

Circulating dp-uc MGP

Four studies reported a decrease in mean dp-uc MGP concentration (5, 11, 15, 17). One study (11) reported mean dp-uc MGP concentration that significantly reduced after MK7 supplementation, with a 55.1% relative reduction in dp-uc MGP

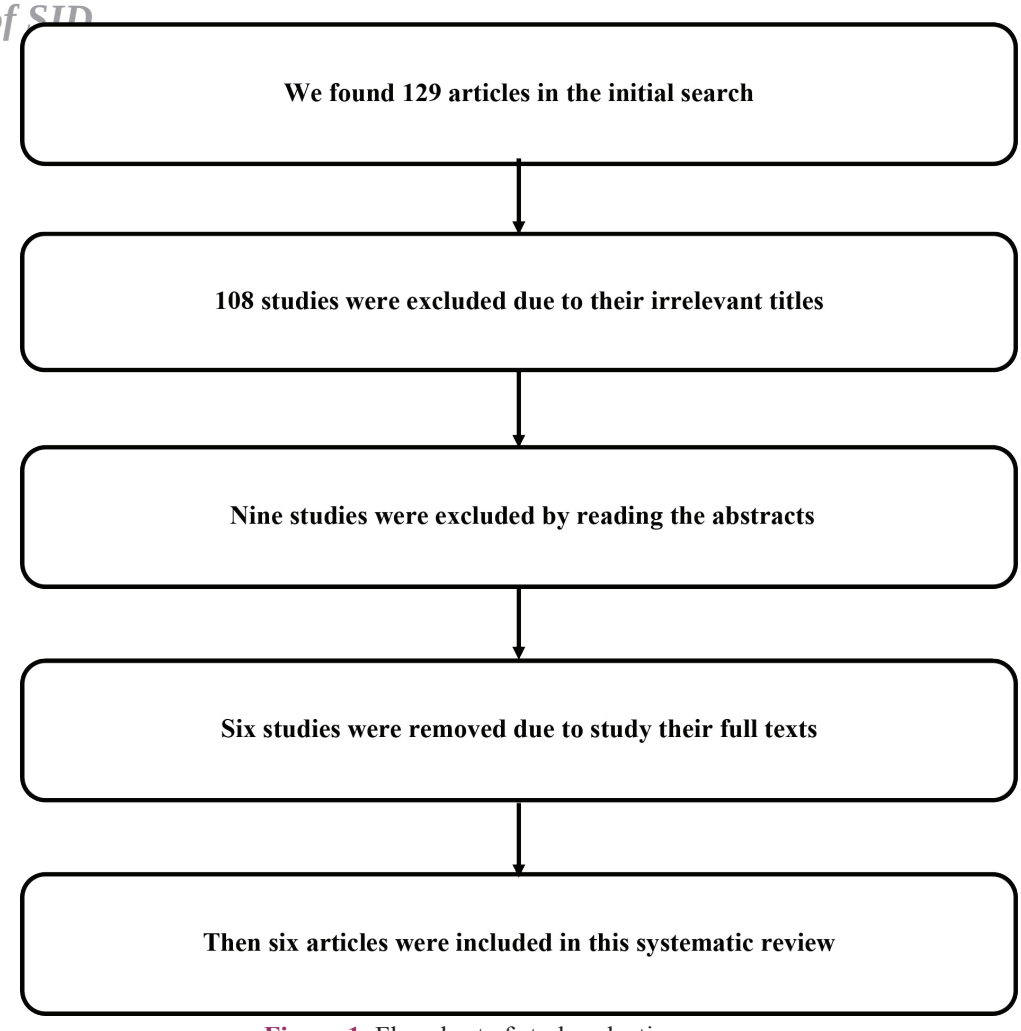

Figure 1: Flowchart of study selection process.

Table 1: Features of the studies of the effects of vitamin K supplement on artery calcification

Study	Participants	Duration	Intervention vitamin K supplement	Outcomes
Rogier et al., 2014	165 hemodialysis patients	8 weeks	MK7 360 µg/thrice weekly 720 µg/thrice weekly 1080 µg/thrice weekly	Decrease in the dp-uc MGP level
Mansour et al., 2017	60 renal transplant recipients	8 weeks	MK7 360 µg/d	Significantly reduced mean dp-uc MGP concentrations reduction in mean cfPWV.
Westernfeld et al., 2012	103 Long-term hemodialysis patients	7 weeks	MK7 45 µg/d (n=19) 135 µg/d (n=17) 360 µg/d (n=14)	Decrease in circulating dp-uc MGP
Brandenburg et al., 2017	72 patients	12 months	MK4 2mg (once daily orally) (n=38)	Reduction of plasma dp-uc MGP.
Shea et al., 2009	295 men and postmenopausal women	3 years	Phylloquinone 500 µg/d (n=149)	There was no difference in CAC progression between the phylloquinone group and the control group
Ikari et al., 2016	26 patients with at least one coronary risk factor	3 years	MK4 45 mg/day	CAC significantly increased baPWV did not change

MGP: Matrix Gla Protein , CAC score: Coronary Artery Calcification score , PWV: Pulse Wave Velocity , dp-uc MGP: dephosphorylated-uncarboxylated MGP , baPWV: Brachial-ankle pulse wave velocity , cfPWV: Carotid-femoral Pulse Wave Velocity

concentration as compared with the baseline values (556.9 pmol/L vs. 249.7 pmol/L; P<0.0001). A study (15) reported strong correlation between dialysis vintage and baseline dp-uc MGP (P<0.001, r=0.29). After 8 weeks of MK7 supplementation, a significant and dose dependent decrease in the dp-uc MGP level with relative reduction rates (the mean of the percentage decrease of each patient) of 17,33 and 46% was documented in the 360-, 720- and 1080- µg groups, respectively. Another study (5) in hemodialysis patients compared with baseline values reported that after 6 weeks of vitamin K2 supplementation, a dose-dependent decrease was detected in dp-uc MGP plasma levels, with the decreases of 17.9%, 36.7%, and 61.1% in the 45-, 135-, and 360-g groups, respectively. In one study (17), it was demonstrated that plasma dp-uc MGP concentration significantly decreased in the vitamin K group by 45% (P<0.001).

PWV Measurement

In two studies (11, 16), this issue was also noted. One study (16) revealed that the MK4 treatment brachial-ankle pulse wave velocity (baPWV) did not change. Another study (11) among patients who were included in the primary analysis population showed the mean baseline carotid-femoral pulse wave velocity 9.8±2.2 m/s. Compared with baseline measurements, the mean 8 weeks follow-up cfPWV was 8.4±1.5 m/s, demonstrating a significant 1.4 m/s absolute decrease in carotid-femoral pulse wave velocity (cfPWV) (14.2% relative reduction) following MK7 supplementation (P<0.0001).

Discussion

According to the results of some researches on hemodialysis patients and renal transplant recipients, a significant vitamin K deficiency was shown. MK7 supplementation was associated with a reduction in dp-uc MGP concentration, and a positive correlation was present between the reduction in arterial stiffness, a surrogate of early CV disease, and the circulating concentration of dp-uc MGP, a marker of subclinical vascular vitamin K deficiency (11). The linear relationship between MK7 dose and the decrease in dp-uc MGP and the absence of a plateau phase suggested that even higher doses of MK7 may be successful aiming at maximal MGP activation. Thus, these studies emphasized the importance of dose and time dependency of vitamin K supplementation in the carboxylation of vitamin K–dependent proteins (5, 15).

According to the results of some researchers, despite high dose MK4 supplementation, CAC increased +14% annually, but baPWV did not change (−0.7%). CAC similarly increased annually irrespective of baseline vitamin K insufficiency. The MK4 supplementation improved baPWV only in patients with vitamin K insufficiency (18). The effective dose to protect atherosclerosis or calcifications is unknown in terms of arterial stiffness. Long-term use of MK7 supplements improved arterial stiffness in healthy postmenopausal women, especially in women having a high arterial stiffness (12).

The results of this study were similar to prior reports as have little preventive effects on CAC (16). On the other hand, effects on arterial stiffness were also observed in this study. Supplemental vitamin K in less progression of CAC in older men and women who were adherent to the treatment and took vitamin K than in those who did not take vitamin K; of those individuals with pre-existing CAC; showed that those who received phylloquinone had 6% less progression than those who did not. In contrast, vitamin K supplementation did not reduce the development of new CAC, of which there was an annual increase of 5% in both groups (12, 19, 20). The mechanisms by which vitamin K conferred a protective role is still uncertain (21).

Conclusion

Larger studies in other populations are needed to confirm these findings, and to assess the risks and benefits of vitamin K supplementation on clinical CVD.

Conflict of Interest

None declared.

References

1 Bérard E, Bongard V, Ruidavets J, et al. Pulse wave velocity, pulse pressure and number of carotid or femoral plaques improve prediction of cardiovascular death in a population at low risk. *J Hum Hypertens*. 2013;27:529-34. DOI:10.1038/jhh.2013.8. PMID:23426066.

2 Lees JS, Chapman FA, Witham MD, et al. Vitamin K status, supplementation and vascular disease: a systematic review and meta-analysis. *Heart*. 2018. pii: heartjnl-2018-313955. DOI:10.1136/heartjnl-2018-313955. PMID:30514729.

3 Lindholt JS, Frandsen NE, Fredgart MH, et al. Effects of menaquinone-7 supplementation in patients with aortic valve calcification: study protocol for a randomised controlled trial. *BMJ Open*. 2018;8:e022019. DOI: 10.1136/bmjopen-2018-022019. PMID: 30139903.

4 Demer LL, Tintut YJC. Vascular calcification: pathobiology of a multifaceted disease.

Circulation. 2008;117:2938-48. DOI:10.1161/circulationaha.107.743161.

5 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. DOI: 10.1053/j.ajkd.2011.10.041. PMID: 22169620.

6 Danziger J, Young RL, Shea MK, et al. Vitamin K–dependent protein activity and incident ischemic cardiovascular disease: the multi-ethnic study of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2016;36:1037-42. DOI:10.1161/ATVBAHA.116.307273. PMID:27034472.

7 Viegas CS, Rafael MS, Enriquez JL, et al. Gla-rich protein acts as a calcification inhibitor in the human cardiovascular system. *Arterioscler Thromb Vasc Biol*. 2015;35:399-408. DOI:10.1161/ATVBAHA.114.304823. PMID:25538207.

8 Boraldi F, Annovi G, Vermeer C, et al. Matrix gla protein and alkaline phosphatase are differently modulated in human dermal fibroblasts from PXE patients and controls. *J Invest Dermatol*. 2013;133:946-54. DOI:10.1038/jid.2012.460. PMID:23223140.

9 Aghasadeghi K, Zarei-Nezhad M, Keshavarzi A, et al. The prevalence of coronary risk factors in Iranian lor migrating tribe. *Arch Iran Med*. 2008;11:322-5. DOI:08113/AIM.0015. PMID:18426325.

10 Murshed M, Schinke T, McKee MD, et al. Extracellular matrix mineralization is regulated locally; different roles of two gla-containing proteins. *J Cell Biol*. 2004;165:625-30. DOI:10.1083/jcb.200402046. PMID:15184399.

11 Mansour AG, Hariri E, Daaboul Y, et al. Vitamin K2 supplementation and arterial stiffness among renal transplant recipients-a single-arm, single-center clinical trial. *J Am Soc Hypertens*. 2017;11:589-97. DOI:10.1016/j.jash.2017.07.001. PMID: 28756183.

12 Shea MK, O'Donnell CJ, Hoffmann U, et al. Vitamin K supplementation and progression of coronary artery calcium in older men and women. *Am J Clin Nutr*. 2009;89:1799-807. DOI: 10.3945/ajcn.2008.27338. PMID: 19386744.

13 Toto RD, Bahous SA, Stephan A, et al. Aortic stiffness, living donors, and renal transplantation. Commentary. 2006;47.

14 Henein MY, Koulaouzidis G, Granåsen G, et al. The natural history of coronary calcification: A meta-analysis from St Francis and EBEAT trials. *Int J Cardiol*. 2013;168:3944-8. DOI:10.1016/j.ijcard.2013.06.057. PMID:23870639.

15 Caluwe R, Vandecasteele S, Van Vlem B, et al. Vitamin K2 supplementation in haemodialysis patients: a randomized dose-finding study. *Nephrol Dial Transplant*. 2014;29:1385-90. DOI:10.1093/ndt/gft464.

16 Ikari Y, Torii S, Shioi A, et al. Impact of menaquinone-4 supplementation on coronary artery calcification and arterial stiffness: an open label single arm study. *Nutr J*. 2016;15:53. DOI: 10.1186/s12937-016-0175-8. PMID: 27175730.

17 Brandenburg VM, Reinartz S, Kaesler N, et al. Slower progress of aortic valve calcification with vitamin K supplementation: results from a prospective interventional proof-of-concept study. *Circulation*. 2017;135:2081-3. DOI: 10.1161/CIRCULATIONAHA.116.027011. PMID:28533322.

18 Ikari Y, Torii S, Shioi A, et al. Impact of menaquinone-4 supplementation on coronary artery calcification and arterial stiffness: An open label single arm study. *Nutr J*. 2015;15:53. DOI:10.1186/s12937-016-0175-8. PMID:27175730.

19 Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA) . *Circulation*. 2007;115:2722-30. DOI:10.1161/CIRCULATIONAHA.106.674143. PMID:17502571.

20 Kuller LH, Matthews KA, Edmundowicz D, et al. Incident coronary artery calcium among postmenopausal women. *Atherosclerosis*. 2008;200:278-85. DOI:10.1016/j.atherosclerosis.2007.12.057. PMID:18289547.

21 Shea MK, Booth SL, Weiner DE, et al. Circulating Vitamin K Is Inversely Associated with Incident Cardiovascular Disease Risk among Those Treated for Hypertension in the Health, Aging, and Body Composition Study (Health ABC). *J Nutr*. 2017;147:888-95. DOI:10.3945/jn.117.249375. PMID:28356433.