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Vitamin K Supplementation for Reducing Cardiovascular Events in End-Stage Chronic Kidney Disease: A Systematic Review

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ABSTRACT

This study was conducted to analyze the hSIL of Vitamin K Supplementation in Reducing Cardiovascular Events in End-Stage Chronic Kidney Disease: A Systematic Review. Cardiovascular disease (CVD) is the leading source of morbidity and mortality worldwide, and chronic kidney disease (CKD) is a major contributor to this matter. Kidney disease is estimated to affect over 850 million people worldwide. The present systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We searched studies from electronic databases (PubMed Central, ScienceDirect, PLoS One, Google Scholar, Nature). Studies were considered eligible if they met the following criteria: (1) the study is a randomized controlled trial (RCT), (2) the study was published in the last 5 years (2018– 2022), (3) the study participants were adult patients with kidney disease from stage III to end-stage who were given vitamin K supplementation, (4) the study reported coronary artery calcium scores pre- and post- vitamin K supplementation, (5) the study was published in English. Risk of bias of each study was evaluated using Cochrane Risk of Bias (RoB) 2 tool. Data were descriptively examined and narratively reported. In conclusion, our results do not suggest that vitamin K supplementation may affect vascular calcification as measured by the CAC score. Up till now there is no treatment to reverse vascular calcification in ESKD patients. The current clinical practice should focus on prevention and retardation of its progression.

Keywords:

Vitamin K Supplementation, Cardiovascular, End-stage Chronic Kidney Disease

1. INTRODUCTION

Cardiovascular disease (CVD) is the leading source of morbidity and mortality worldwide, and chronic kidney disease (CKD) is a major contributor to this matter. Kidney disease is estimated to affect over 850 million people worldwide [1]. This is due to the altered mineral metabolism that affects the vasculature and results in vascular calcium deposition. Both calcification in the coronary arteries, which is an indication of atherosclerotic plaque, and calcification in the peripheral arteries, a symptom of more widespread mineral imbalances that may result in arterial stiffening, are frequently found in CKD patients [2].

Vitamin K is a fat-soluble vitamin that plays many significant roles in human body physiology. Perhaps vitamin K's most well-known activity is its part in coagulation. Vitamin K is also essential for the control of glycemic status because it lowers the risk of getting diabetes mellitus and improves insulin sensitivity. Vitamin K is necessary for the synthesis and operation of osteocalcin, a protein responsible for bone formation [3]. As a result, vitamin K has a number of functions in the body, some of which necessitate further study to determine their applicability in practical situations [4].It was previously found that supplementing with vitamin K may delay this process and prevent atherosclerosis [5]. Vitamin K is found to is essential for the stimulation of extrahepatic -carboxyglutamate (Gla)

proteins like matrix Gla protein (MGP), a small protein with 84 amino acids and a molecular weight of 14 kDa that is regarded as the most potent inhibitor of vascular calcification. The likelihood of cardiovascular disease (CVD) is thought to be independently predicted by vitamin K deficiency [6].

Over the years, as more evidence has appeared to support a role for vitamin K deficiency in vascular classification, the notion that vitamin K supplementation could slow the rapid progression of vascular classification in CKD patients has gained momentum, although with contradicting results [7]. The present study's objective is to assess the impact of vitamin K supplementation on CAC scores in CKD patients [8].

2. METHODS

The present systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We searched studies from electronic databases (PubMed Central, ScienceDirect, PLoS One, Google Scholar, Nature). The search terms used were 5 vitamin K supplementation, chronic kidney disease, end-stage kidney disease and coronary artery calcium score. References from all retrieved studies were manually searched for relevant articles. Studies were considered eligible if they met the following criteria : (1) the study is a randomized controlled trial (RCT), (2) the study was published in the last 5 years (2018– 2022), (3) the study participants were adult patients with kidney disease from stage III to end-stage who were given vitamin K supplementation, (4) the study reported coronary artery calcium scores pre- and post- vitamin K supplementation, (5) the study was published in English [9]. Studies are excluded if (1) the study was non-randomized, (2) full-text version of the study was not accessible, (3) relevant outcomes were not reported, (4) the study was published before 2018.. Data were independently extracted from each study by a reviewer. Any disagreement was resolved by discussion between authors [10]. Extracted components include first author of the study, year of study, location of the study, study setting, number of participants, intervention and control measures, results and conclusion of the study. Risk of bias of each study was evaluated using Cochrane Risk of Bias (RoB) 2 tool. Data were descriptively examined and narratively reported [11].

3. RESULTS AND DISCUSSION

Study Characteristics

Based on 3 databases, we extracted 1,333 studies. After making a duplicated selection and using the filter option on each database, the remaining 1,245. After screening titles and abstracts, we excluded 1,223 studies leaving 22 literatures. We evaluated the available full text articles and found 4 studies that were used. From 4 RCT studies, there were 280 samples [12]. The characteristics of the studies are shown in Table 1. All studies were RCTs conducted in hospitals and clinical trials in patients with stage III to end-stage chronic kidney disease who were on dialysis [13]. Patients received vitamin K supplementation compared to the control group for 12 months to 24 months and measurements were taken at the end of vitamin K supplementation. Meta-analysis were not possible to be conducted due to significant heterogenicity in data reporting and variable interventions between studies. All included studies were considered low-risk, as seen from Table 2.

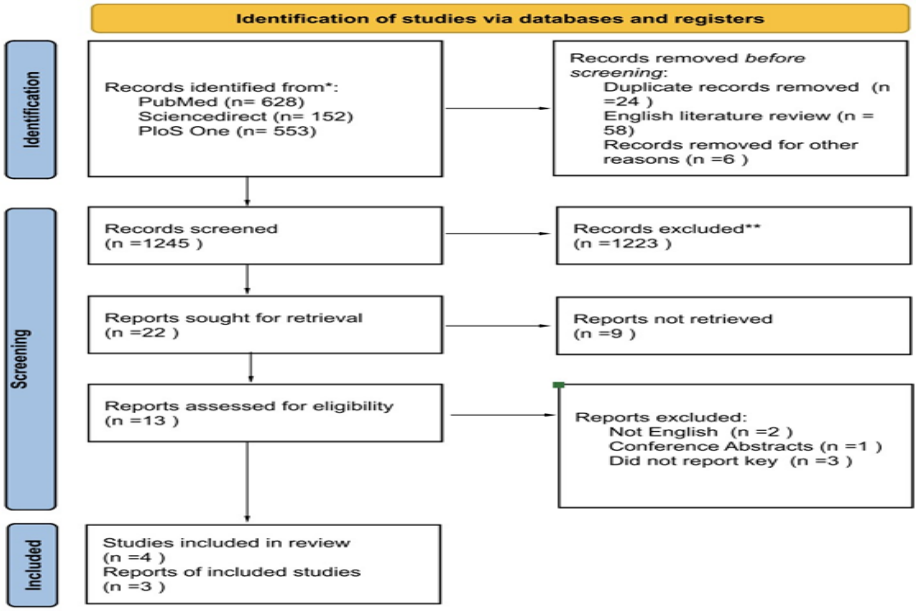

Figure 1. Study Flowchart

Effect of Vitamin K on CAC score

A study conducted by Lees et al (2020), vitamin K administration three times a week for 1 year found a therapeutic effect on vascular rigidity and vascular calcification were not significant (-23 (95% CI -0.75 to 0.29) x 10-3 mmHg-1, p value 0.377; -141 (95% CI -320 to 38) units, p value 0.124). The results of the CACS measurement after the intervention found that the vitamin K group was not significant with a value of 460 units compared to placebo of 412 units (p-value 0.120) and also during the study, there was an incidence of disease in 68.9% of patients [14].

Research conducted by Mosa et al. in 2020 in Egypt with an RCT giving phytomenadione for 1 year and measuring calcification in the abdominal aorta and MGP levels. The results showed that MGP levels increased significantly in patients with end-stage kidney disease who received vitamin K supplementation compared to the group who did not receive vitamin K supplementation (75.76±26 pg/dl vs 49.36±6 pg/dl ;p <0.005). there was no change in CIMT and AACS levels in the vitamin K group, but there was a significant increase in CIMT and AACS in the placebo group [15].

Research conducted by Oikonomaki et al, 2019 measured uc-MGP levels which act as inhibitors of vascular calcification in CKD patients who received vitamin K2 supplementation for one year showed a significant decrease in uc-MGP levels by 47% compared to the control group which experienced an increase of 12%. (p = 0.005). However, the value of AGATSTON in assessing aortic calcification in both groups continued to increase significantly. There is a study with dp-ucMGP plasma measurement by Schousboe et al. In an RCT on patients undergoing dialysis and given vitamin K, the results showed a decrease in dp-ucMGP plasma by 40% and the Agatston score experienced a significant increase, so this study is the same as previous studies that have been conducted.

No.	Author	Year	Location	Study setting	Study design	Sample Size	Sample Characteristics	Intervention	Control	Results (HR, OR, RR)	Conclusion
1.	Lees et al	2020	UK	Clinical trial	RCT	90	Age 56.3 (7.8) 32% male eGFR 52.4 (21.6)	Menadiol diphosphate 5 mg, 3x/week, for a year	Placebo	CAC (coronary artery calcium score) difference 28 (0-65) vs 33 (0-87) Adjusted treatment effect −141 (−320 to 38) (p= .120)	There was no impact of vitamin K on vascular stiffness
2.	Mosa et al.	2020	Egypt	Hospital	RCT	40	Age 50.2 (8.5) Male 45% Duration of HD 74± 41 months	Phytomenadione 10 mg, after each session of HD, for a year	Placebo	AACS (abdominal aorta calcification score) 6±2. vs 7.2±2.2 5 (p >0.05)	There were no significant changes in AACS in Vitamin K group after vitamin K supplementation
3.	Oikonomaki et al.	2019	USA	Clinical trial	RCT	102	Age 70.09 ± 12.68 year Male Duration of dialysis 8.38 ± 5.96 years	Vitamin K2 [menaquinone-7 (MK-7)] 200 mcg daily, for one year	Placebo	CAC score (Agaston) 10,412.53 ± 7227.2 (p= 0.02) vs 11,036.58 ± 9053. 0.01 34 (p=0.01)	Oral administration of vitamin K2 did not have an effect in the progression of aortic calcification.
4.	Schousboe et al.	2021	Denmark	Hospital	RCT	48	Age 62 (611) years Males 79% Duration of dialysis 28 (7) months	Vitamin K, MK-7, 360 µg daily, for two year	Placebo	AACS score mean change 1.1 (- 0.5 to 2.7, p= 0.19)	Vitamin K supplementation improved vitamin K status, but did not hinder or modify the progression of arterial calcification in dialysis patients.

Table 2. Risk of Bias Assessment

No.	Author	Randomization process	Deviations from the intended interventions		Missing outcome data	Measurement of the outcome	Selection of the reported result
			Effect of assignment to intervention	Effect of starting and adhering to intervention			
1	Lees et al.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2.	Mosa et al	High risk	Some concerns	Some concerns	Some concerns	Some concerns	Low risk
3.	Oikonomaki et al.	High risk	Low risk	Some concerns	Low risk	Low risk	Low risk
4.	Schousboe et al.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Discussion

One of the leading causes of mortality and morbidity in CKD patients are cardiovascular diseases, due to the increased risk of vascular calcification. This is demonstrated by the findings that an elevated risk of cardiovascular diseases was identified in more than 50% of dialysis patients, whether receiving hemodialysis or peritoneal dialysis. Intimal and medial calcium, hardening of the cardiac valves, and calciphylaxis are all common forms of arterial calcification in CKD [16]. Calciphylaxis, also known as calcific uremic arteriolopathy, is an uncommon condition that most frequently affects uremic patients and involves calcification of the small vessels located within the lower layers of the skin as well as fatty tissue and cutaneous necrosis [12]. Vascular calcification was once thought to be an passive process, but it is now clear that it is actually an active process caused by an imbalance between the calcification promoters and inhibitors. Reduced amounts of calcification inhibitors brought on by the uraemic environment and chronic micro-inflammation were found to hasten this process in CKD patients [17].

Vitamin K is a fat-soluble vitamin that is involved in many physiological functions in the body. One of the most well-known function of vitamin K is the regulation of coagulation, bone and vascular health. (Roumeliotis et al, 2021) The regulation of this process depends heavily on proteins that are reliant on vitamin K. Matrix Gla protein (MGP) and Gla-rich protein, two significant proteins that control and prevent arterial calcium, need vitamin K as a cofactor for gamma-carboxylation, a crucial stage in their activation [18].

MGP is a small protein that is primarily synthesized by chondrocytes, osteoclasts, and vascular smooth muscle cells. MGP activation depends on two post-translational processes, which are glutamate carboxylation, which is reliant on vitamin K, and serine phosphorylation. MGP activation then produces calcification inhibitory action by inhibiting local crystal growth and smooth muscle cell apoptosis. In vitamin K deficiency, the in- active form of MGP , dephosphorylated, uncarboxylated MGP (dp-ucMGP) is released into the bloodstream. Both in vitro and animal studies convincingly demonstrated that dp-ucMGP aggregates at sites of arterial calcification [19]. Therefore, dp-ucMGP level is a key marker of vitamin K insufficiency that is associated with vascular calcification. Coronary artery calcium scoring, also referred to as the CAC score, is one of the most frequently used techniques to evaluate arterial calcification and stiffness. The CAC score is an effective risk-assessment tool for risk stratification in coronary artery disease [20]. The Agatston score is most frequently used to quantify coronary calcium on CT. (Parikh et al, 2018) Supplementation of vitamin K has been previously associated with a dose-dependent reduction in circulating dp-ucMGP and improved arterial stiffness among healthy adults CKD patients. (Mansour et al, 2017) While many studies have assessed the levels of dp-ucMGP and MGP, not many studies have evaluated the effects of vitamin K supplementation on CAC score, which became the aim of our study. The journals included in our study

found contradicting results regarding usefulness of vitamin K supplementation in CKD patients in regards to their CAC score. This may be caused by many factors [21]. Lees et al stated that, an excess of calcification regulators and inhibitors, as well as exposure to numerous risk factors, all contribute to the development of vascular calcification. [22]Multiple factors can affect vitamin K stores in CKD patients, and the main causes of its deficiency include food restriction, uraemia-associated dysbiosis, and drugs. Since leafy green vegetables and fermented products are the main source of vitamin K, a vitamin K deficiency may be a sign of long-term exposure to an unhealthy diet and/or way of life. Supplementing with vitamin K may not be sufficient to undo the impacts of vascular injury that has been sustained over a lifetime. An early, comprehensive prophylactic approach might be more effective. However, Lees et al did not monitor baseline vitamin K levels and included patients with heterogenous calcification profiles [23]. Therefore, it is possible that the vitamin K supplementation would be beneficial for patients with clear evidence of vitamin K deficiency. Due to different calcification profiles, vitamin K supplementation would have given variable effects [24]. In the ViKTORIES trial, treatment was only given for a year. Lees et al stated that it is possible that longer treatment is required to see a difference, particularly if used to reduce progression of vascular stiffness, rather than in- duce regression of existing disease. However, Levy-Schousboe et al, whose intervention was given for 2 years, also did not produce significant results regarding progression of arterial calcification, eventhough vitamin K status were improved [25]. Oikonomaki et al also did not found any effect of oral administration of vitamin K2 on progression of aortic calcification. Eventhough they found lower blood uc-MGP levels, which theoretically should have an impact on vascular calcification, CAC score was not found to be significantly different. This means that vitamin K supplementation does not appear to be sufficient to stop the development of vascular calcification, and supports a multifactorial pathophysiologic process [26]. It is possible that the overall mass of macrocalcification (i.e., volume and density) identified by conventional CT does not accurately represent active calcification (i.e., microcalcification) in susceptible atherosclerotic plaques [27].

Similar results were found by Mosa et al., where after one-year of vitamin K supplementation, a significant increase in MGP levels in Vitamin K group were noticed but there were no significant changes in carotid intimal medial thickness (CIMT) and abdominal aorta calcification score (AACS) after vitamin K supplementation in compared to their baseline levels. (Mosa et al) Although this impact is potentially beneficial, it does not appear to be sufficient to stop the development of vascular calcification, a multifactorial pathophysiologic process [28]. Though supplementing with Vitamin K2 did not result in clinically meaningful vascular calcification reversal, its safe administration profile makes it a contender for widespread nutritional fortification in all dialysis patients. Larger studies are needed to confirm whether preventive vitamin K2 sup- plementation is warranted in ESRD patients [29].

Our study did not find significancy in vitamin K supplementation in altering vascular calficication. Similar results were found by Geng et al, which assessed the effects of vitamin K on pulse wave velocity (PWV), a parameter that reflects vascular elasticity that also measures the degree of vascular stiffness. A meta-analysis of 10 RCTs did not produce favorable results in line with the use of vitamin K. (Geng et al, 2022) There are some limitations in our study that should be highlighted. First, the number of included studies are relatively small. Second, the substantial variation in findings reporting across included studies precluded the use of meta-analysis. To further assess the use of vitamin K in CKD patients to avoid vascular calcification, future research should incorporate more pertinent studies and conduct a meta-analysis [30].

4. CONCLUSION

In conclusion, our results do not suggest that vitamin K supplementation may affect vascular calcification as measured by the CAC score. Up till now there is no treatment to reverse vascular calcification in ESKD patients. The current clinical practice should focus on prevention and retardation of its progression.

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