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Subclinical atherosclerosis is linked to small intestinal bacterial overgrowth via vitamin K2-dependent mechanisms.

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Abstract

AIM: To assess the rate of matrix Gla-protein carboxylation in patients with small intestinal bacterial overgrowth (SIBO) and to decipher its association with subclinical atherosclerosis.

METHODS: Patients with suspected SIBO who presented with a low risk for cardiovascular disease and showed no evidence of atherosclerotic plaques were included in the study. A glucose breath test was performed in order to confirm the diagnosis of SIBO and vascular assessment was carried out by ultrasound examination. Plasma levels of the inactive form of MGP (dephosphorylated-uncarboxylated matrix Gla-protein) were quantified by ELISA and vitamin K2 intake was estimated using a food frequency questionnaire.

RESULTS: Thirty-nine patients were included in the study. SIBO was confirmed in 12/39 (30.8%) patients who also presented with a higher concentration of dephosphorylated-uncarboxylated matrix Gla-protein (9.5 μg/L *vs* 4.2 μg/L; $P = 0.004$). Arterial stiffness was elevated in the SIBO group (pulse-wave velocity 10.25 m/s *vs* 7.68 m/s; $P = 0.002$) and this phenomenon was observed to correlate linearly with the levels of dephosphorylated-uncarboxylated matrix Gla-protein ($\beta = 0.220$, $R^2 = 0.366$, $P = 0.03$). Carotid intima-media thickness and arterial calcifications were not observed to be significantly elevated as compared to controls.

CONCLUSION: SIBO is associated with reduced matrix Gla-protein activation as well as arterial stiffening. Both these observations are regarded as important indicators of subclinical atherosclerosis. Hence, screening for SIBO, intestinal decontamination and supplementation with vitamin K2 has the potential to be incorporated into clinical practice as additional preventive measures.

KEYWORDS: Atherosclerosis; Cardiovascular disease risk; Dysbiosis; Small intestinal bacterial overgrowth; Vitamin K

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Circulating uncarboxylated matrix Gla protein, a marker of vitamin K status, as a risk factor of cardiovascular disease.

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Abstract

OBJECTIVES: Vitamin K plays a pivotal role in the synthesis of Matrix Gla protein (MGP), a calcification inhibitor in vascular tissue. Vascular calcification has become an important predictor of cardiovascular disease. The aim of the current study was to examine the potential association of circulating desphospho-carboxylated and -uncarboxylated MGP (dp-cMGP and dp-ucMGP), reflecting vitamin K status, with the incidence of cardiovascular events and disease (CVD) in older individuals.

STUDY DESIGN: The study was conducted in 577 community-dwelling older men and women of the Longitudinal Aging Study Amsterdam (LASA), aged >55 year, who were free of cardiovascular disease at baseline. Multivariate Cox proportional hazards models were used to analyze the data.

MAIN OUTCOME MEASURES: Incidence of CVD.

RESULTS: After a mean follow-up of 5.6±1.2 year, we identified 40 incident cases of CVD. After adjustment for classical confounders and vitamin D status, we observed a more than 2-fold significantly higher risk of CVD for the highest tertile of dp-ucMGP with a HR of 2.69 (95% CI, 1.09-6.62) as compared with the lowest tertile. Plasma dp-cMGP was not associated with the risk of CVD.

CONCLUSIONS: Vitamin K insufficiency, as assessed by high plasma dp-ucMGP concentrations is associated with an increased risk for cardiovascular disease independent of classical risk factors and vitamin D status. Larger epidemiological studies on dp-ucMGP and CVD incidence are needed followed by clinical trials to test whether vitamin K-rich diets will lead to a decreased risk for cardiovascular events.

KEYWORDS: CVD; Cardiovascular disease; Gla; LASA; Longitudinal Aging Study Amsterdam; MGP; Matrix Gla-protein; Vitamin K status; cardiovascular events and disease; desphospho-carboxylated MGP; desphospho-uncarboxylated MGP; dp-cMGP; dp-ucMGP; matrix Gla protein; γ-carboxyglutamate

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Vitamin K supplementation and progression of coronary artery calcium in older men and women[1,2,3,4]

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Abstract

Background: Coronary artery calcification (CAC) is an independent predictor of cardiovascular disease. A preventive role for vitamin K in CAC progression has been proposed on the basis of the properties of matrix Gla protein (MGP) as a vitamin K–dependent calcification inhibitor.

Objective: The objective was to determine the effect of phylloquinone (vitamin K1) supplementation on CAC progression in older men and women.

Design: CAC was measured at baseline and after 3 y of follow-up in 388 healthy men and postmenopausal women; 200 received a multivitamin with 500 μg phylloquinone/d (treatment), and 188 received a multivitamin alone (control).

Results: In an intention-to-treat analysis, there was no difference in CAC progression between the phylloquinone group and the control group; the mean (±SEM) changes in Agatston scores were 27 ± 6 and 37 ± 7, respectively. In a subgroup analysis of participants who were ≥85% adherent to supplementation (n = 367), there was less CAC progression in the phylloquinone group than in the control group (P = 0.03). Of those with preexisting CAC (Agatston score > 10), those who received phylloquinone supplements had 6% less progression than did those who received the multivitamin alone (P = 0.04). Phylloquinone-associated decreases in CAC progression were independent of changes in serum MGP. MGP carboxylation status was not determined.

Conclusions: Phylloquinone supplementation slows the progression of CAC in healthy older adults with preexisting CAC, independent of its effect on total MGP concentrations. Because our data are hypothesis-generating, further studies are warranted to clarify this mechanism. This trial was registered at clinicaltrials.gov as NCT00183001.

INTRODUCTION

Coronary artery calcification (CAC) is an independent predictor of cardiovascular disease (CVD) and CVD-related mortality (1–3). Matrix Gla protein (MGP) is a vitamin K–dependent protein that functions as a calcification inhibitor (4) and may be integral in the regulation of human vascular mineralization (5, 6). Vitamin K is required for the function of MGP through its role as an enzyme cofactor in the γ-carboxylation of the protein. Vitamin K antagonism with warfarin inhibits the vitamin K–dependent carboxylation of MGP, which leads to arterial calcification in rats (7). Furthermore, diets high in vitamin K have been shown to reverse aortic calcification and improve arterial elasticity in warfarin-treated rats (8).

Our current understanding of the potential role of vitamin K intake in protecting against vascular calcification in humans is limited. An inverse cross-sectional association between menaquinone-4 (MK-4, or vitamin K2) intake and arterial calcification was reported (9), whereas no associations between intake of phylloquinone, the primary dietary source of vitamin K, and abnormal calcification were noted (9, 10). In a single randomized controlled trial that assessed the effect of phylloquinone on vascular health in postmenopausal women, supplementation

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Vitamin K Status and Vascular Calcification: Evidence from Observational and Clinical Studies[1,2]

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Abstract

Vascular calcification occurs when calcium accumulates in the intima (associated with atherosclerosis) and/or media layers of the vessel wall. Coronary artery calcification (CAC) reflects the calcium burden within the intima and media of the coronary arteries. In population-based studies, CAC independently predicts cardiovascular disease (CVD) and mortality. A preventive role for vitamin K in vascular calcification has been proposed based on its role in activating matrix Gla protein (MGP), a calcification inhibitor that is expressed in vascular tissue. Although animal and in vitro data support this role of vitamin K, overall data from human studies are inconsistent. The majority of population-based studies have relied on vitamin K intake to measure status. Phylloquinone is the primary dietary form of vitamin K and available supplementation trials, albeit limited, suggest phylloquinone supplementation is relevant to CAC. Yet observational studies have found higher dietary menaquinone, but not phylloquinone, to be associated with less calcification. Vascular calcification is highly prevalent in certain patient populations, especially in those with chronic kidney disease (CKD), and it is plausible vitamin K may contribute to reducing vascular calcification in patients at higher risk. Subclinical vitamin K deficiency has been reported in CKD patients, but studies linking vitamin K status to calcification outcomes in CKD are needed to clarify whether or not improving vitamin K status is associated with improved vascular health in CKD. This review summarizes the available evidence of vitamin K and vascular calcification in population-based studies and clinic-based studies, with a specific focus on CKD patients.

Introduction

Vascular calcification occurs when vessel and/or valvular tissue becomes mineralized. In the vessel wall, calcium deposition can occur in the intimal and/or medial layers. Calcification of the intimal layer is reflective of atherosclerotic heart disease. Calcium deposition in the intimal layer of the coronary arteries (known as CAC[5]) can lead to vascular occlusion. It is detectable in ~30% of adults without clinical CVD (1–4) and is incrementally predictive of future cardiovascular events and overall mortality, independent of traditional CVD risk factors (5–7). Certain patient groups, especially those with CKD, are at greater risk for CAC (8–10).

In 2004, it was determined that 11% of the general population in the United States had CKD, translating into >19 million affected people (11). CKD is defined as the presence of kidney damage with or without reduced kidney function (12). The severity of CKD is determined by a staging process that is based on an estimated glomerular filtration rate. Moderate to severe CKD (stages 3–5) is represented by an estimated glomerular filtration rate of <60, <30, and <15 mL/(min·1.73 m^2), respectively, and stage 5b encompasses those individuals who require a form of kidney replacement therapy (hemodialysis, peritoneal dialysis, or kidney transplant) (12).

At every stage of CKD, the leading cause of mortality is CVD and patients are more likely to die of a cardiac event than they are to ever require a form of kidney replacement therapy (13). CKD patients are particularly prone to medial calcification (known as Monckeberg's sclerosis), which leads to arterial stiffening, elevated systolic pressure, and increased cardiac workload (14, 15). Medial calcification is predictive of cardiovascular and all-cause mortality in CKD patients, independent of intimal calcification and CVD risk factors (16, 17). Calcific uremic arteriopathy, also known as calciphylaxis, is unique to patients with ESKD and