Cardiovascular Diseases and Fat Soluble Vitamins: Vitamin D and Vitamin K

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Summary Recently, the associations between insufficiency of fat soluble vitamins and cardiovascular diseases (CVDs) have been reported. Vitamin D affects the cardiovascular system via several pathways, such as suppression of parathyroid hormone, the renin-angiotensin-aldosterone system and vascular endothelial growth and the immune system. Cross-sectional and longitudinal studies have shown the association between the concentration of serum 25-hydroxyvitamin D (25OHD), which is a vitamin D metabolite indicating nutritional vitamin D status, and hypertension, myocardial infarction, heart failure and CVD mortality. On the other hand, the association between vitamin K status and CVDs, especially vascular calcification, has been also reported. Cross-sectional and cohort studies show that high vitamin K status is associated with reduced coronary artery calcification, CVDs and mortality risk. Epidemiological and basic studies indicate that vitamin K possesses a benefit in the prevention of the progression of coronary artery calcification via activation of matrix-gla protein (MGP). While these data in epidemiological and basic studies suggest the protective role of vitamin D and K in CVDs, the benefits of supplementation of both vitamins have not been validated in randomized controlled trials. Further basic and interventional studies are needed to confirm the benefit of both vitamins in protection against CVDs.

Key Words vitamin D, vitamin K, cardiovascular disease, fat-soluble vitamins, mortality

1. Vitamin D and Cardiovascular Disease

Background Vitamin D plays an essential role in calcium and bone metabolism. We obtain vitamin D from sunlight exposure and foods, such as fatty fish or fortified dairy products. Vitamin D is activated by 2-step hydroxylation. The 25-hydroxylation of vitamin D in the liver is the initial step, which produce 25OHD. The 1alpha-hydroxylation in the second step, producing 1alpha,25-dihydroxyvitamin D (1,25(OH)2D), which is the active form of vitamin D. The biological actions of vitamin D are expressed by 1,25(OH)2D via binding with vitamin D receptor (VDR). Since the VDR binding affinity of 25OHD is approximately 1/500 that of active vitamin D, 25OHD is not considered to be an active form of vitamin D. However, serum 25OHD concentration is used as the most appropriate marker to assess nutritional vitamin D status. Suboptimal 25OHD concentration induces the elevation of parathyroid hormone (PTH) concentration, and increases the risk of fracture, CVDs, hypertension, mortality, cancer and immunological disorders. Usually, less than 50 nmol/L of serum 25OHD concentration is considered to be a suboptimal vitamin D status.
**Epidemiological studies**

The association between suboptimal vitamin D status and increased risk of CVDs and its related mortality has been supported by data from cross-sectional and prospective cohort studies. In the cross-sectional study, the association between serum 25OHD and CVDs was examined using data from NHANES 2001 to 2004 (n=8,351) (3). In this study, serum 25(OH)D concentrations were divided into 3 categories (≥ or =75, 50 to 72.5, and < 50 nmol/L), and hypovitaminosis D was defined as vitamin D < 50 nmol/L. The burden of CVDs (coronary heart disease, stroke and peripheral arterial disease) increased with lower 25OHD categories. In a nested case-control study (n=18,225) in the Health Professionals Follow-up Study, low levels of 25OHD (≤37.5 nmol/L) were associated with higher risk of myocardial infarction in a graded manner (4).

Liew at al. reported that among patients presenting for coronary angiography, low serum 25OHD concentrations were associated with the presence and extent of angiographic coronary arterial disease but not arterial stiffness or peripheral arterial disease (5). In the Framingham Offspring Study (n=1,739), which is 5.4-year follow-up cohort study, lower than 37.5 nmol/L of 25OHD concentration was associated with incidence of CVDs (HR1.62, 95%CI 1.11–2.36), and this effect was evident in participants with hypertension (HR 2.13, 95%CI 1.30 to 3.48) (6).

In the assessment of the association between mortality and vitamin D status, Dobnig et al. conducted a prospective cohort study (n=3,258) and reported that low 25OHD and 1,25(OH)2D concentrations were independently associated with all-cause and cardiovascular mortality (7). In the NHANES III study, Ginde et al. also reported that low serum 25OHD concentrations had an independent, inverse association with CVD and all-cause mortality (8). Recently, a large cohort study conducted in the UK suggests that plasma 25OHD concentrations predict subsequent lower 13-y total mortality and incident cardiovascular disease, and the lowest risks for mortality were in subjects with concentrations >90 nmol/L (9). In the assessment of the association between hypertension or arterial stiffness and vitamin D status, the larger cohorts show the incident hypertension risks were 2.31 for men and 1.57 for women in the lowest 25OHD concentration group (<37.5 nmol/L) compared to highest group (>75 nmol/L) (10). On the other hand, Uemura et al. reported that the inverse association between dietary calcium intake and brachial-ankle pulse wave velocity (ba-PWV) was striking in subjects with higher dietary vitamin D intake. However, no association was found in subjects with lower dietary vitamin D intake. Thus, they concluded that adequate dietary calcium and vitamin D intakes may be protective against the development of arterial stiffness in Japanese men (11).

**Mechanism of vitamin D function in prevention of CVDs**

While the mechanisms of vitamin D function in CVDs have not been revealed completely, hypothesized mechanisms have been reported in modulation of the renin-angiotensin axis (12), vascular smooth-muscle function (13), nitric oxide (14) or immune function (15). VDR and CYP27B1 (25OHD-1alpha-hydroxylase) gene knockout mice are hypertensive and both express the elevation of renin production in the kidney (16). Plasma ANG II concentrations in both knockout mice also increase. The liganded VDR interacts with cyclic AMP response element binding protein (CREB), thereby preventing its association with the CRE in the mouse renin gene promoter and directly suppressing renin gene transcription (17). Takeda et al. showed that oral active vitamin D reduced atherosclerotic lesion, macrophage accumulation and CD4+ T-cell infiltration in the aorta of ApoE gene knockout mice (18).

2. **Vitamin K and Cardiovascular Disease**

**Background**

Vitamin K is a cofactor of the enzyme responsible for converting specific glutamyl residues to γ-carboxyglutamyl residues in a limited number of blood coagulation factors, bone-related proteins and vascular calcification inhibitors, such as prothrombin, osteocalcin (OC) and matrix gla protein (MGP). MGP is secreted by chondrocytes and vascular smooth muscle cells in the arterial media, and plays a role of inhibition of calcium precipitation and crystallization in the vessel wall. MGP exerts its activity after γ-glutamyl carboxylation, and activated MGP probably exerts an anticalcification function via the antagonizing of bone morphogenetic protein-2 (BMP-2), which regulates osteoblast differentiation (18). Therefore, insufficiency of vitamin K is likely to increase the vascular calcification risk. Serum protein induced by vitamin K absence II (PIVKA-II), undercarboxylated OC(ucOC) and uncarboxylated MGP (ucMGP) concentrations are useful makers to assess vitamin K deficiency in the liver, bone and vascular smooth muscle, respectively. Serum desphosphorylated-ucMGP(dp-ucMGP) concentration is also used as a marker reflecting vitamin K status in vascular smooth muscle and vascular calcification.

**Epidemiological studies**

Observational studies have shown that high vitamin K intake is associated with reduced coronary artery calcification and CVD risk (19). Cardiovascular diseases account for half of all deaths in chronic kidney disease (CKD). Keyzer et al. reported on vitamin K status and mortality after kidney transplantation (n= 518) in a cohort study (20). Plasma dp-ucMGP concentration was used as a marker reflecting vitamin K status. Ninety-one percent of patients were experiencing vitamin K insufficiency (defined as dp-ucMGP≥ 500 pmol/L). Patients in the highest quartile of dp-ucMGP were at considerably higher mortality risk compared with patients in the lowest quartile (HR 3.10; 95% CI, 1.87—5.12). Moreover, the correlation between serum dp-ucMGP concentration and vascular calcification in a cohort of hemodialysis patients (21), and mortality risk in patients with chronic stable vascular disease (22) were reported. These results suggest that vitamin K insufficiency is associated with increased risk of cardiovascular mortal-
ity. To determine the optimal dose of menaquinone–7 (MK-7) for MGP activation, an intervention study was conducted in 200 chronic haemodialysis patients. In this study, patients received 360, 720 or 1,080 μg of MK-7 thrice weekly for 8 wk. Supplementation of pharmacological doses of MK-7 reduced serum dp-ucMGP in a dose-dependent manner. This result suggests that vitamin K supplementation may be a novel approach to prevent vascular calcifications in CKD.

**Future perspectives and conclusion**

The associations between insufficiency of fat-soluble vitamins and CVDs or mortality have been revealed by epidemiological studies. However, despite epidemiological data suggesting a protective role of fat-soluble vitamins in CVDs, the benefits of supplementation of fat-soluble vitamins have not been well validated in randomized controlled trials. Further basic and interventional studies are needed to confirm the benefit of fat-soluble vitamins in protection against CVDs.

**REFERENCES**


