

# Science Review: Vitamins D and K

## Research Highlights

- ✓ Vitamin D is important for calcium homeostasis, bone mineralization, and promoting immune and cardiovascular function.<sup>1</sup>
- ✓ Vitamin K is important in blood coagulation, and plays a central role in decreasing calcium accumulation in the smooth muscles of vascular walls.<sup>2</sup>
- ✓ Vitamins D and K have a synergistic relationship since vitamin D positively impacts the production of vitamin K-dependent bone proteins to induce bone formation and reduce vascular calcification.<sup>3</sup>

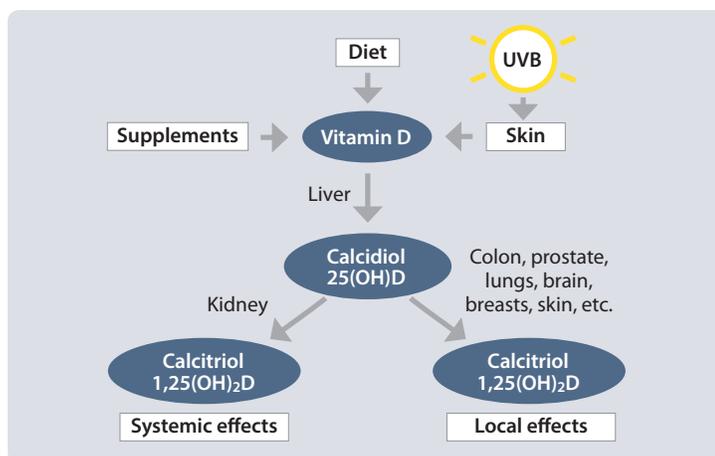
## Vitamin D

Vitamin D is an essential, fat-soluble vitamin that acts as a steroid hormone and plays a central role in many components of our skeletal and extraskeletal health. Vitamin D is naturally present in some fish, mushrooms, and eggs; in select fortified foods such as milk products; and also in the form of dietary supplements and pharmaceuticals. It is also synthesized in the skin from 7-dehydrocholesterol when exposed to ultraviolet B (UVB) rays from sunlight.<sup>1</sup>

There are two forms of vitamin D: D<sub>2</sub> (ergocalciferol) obtained from plants, mushrooms, and yeast; and D<sub>3</sub> (cholecalciferol) obtained from animal products such as fatty fish, fish liver oil, egg yolk, and beef liver.<sup>4</sup>

Vitamin D obtained from food, supplements, or sunlight is considered a prohormone that is biologically inactive. It must undergo two separate hydroxylations in the body for the activation to occur and function as a hormone. The first hydroxylation occurs in the liver by the enzyme 25-hydroxylase where it is hydroxylated to form 25-hydroxyvitamin D (25(OH)D), or calcidiol.<sup>1,4-6</sup> This is the major circulating form of vitamin D and is used as the clinical measure for serum vitamin D status. The second hydroxylation reaction occurs in the kidney by the enzyme 1- $\alpha$ -hydroxylase to form 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D), or calcitriol, its active form.<sup>1,4-6</sup> Vitamin D-binding protein transports vitamin D and its hydroxylated forms in the blood to target tissues.

## Vitamin D in the Body



## Functions of vitamin D

Vitamin D plays a major role in regulating calcium metabolism by increasing intestinal calcium absorption and maintaining adequate levels of calcium in the blood.<sup>5,6</sup> It also maintains adequate phosphorus levels in the body, which together with calcium, aids in bone growth and remodeling as well as normal mineralization of bone.<sup>5,6</sup> Along with these indirect effects on bone, the active form of vitamin D is involved directly in bone cell functions.

Some extraskeletal functions of vitamin D include immune and cardiovascular function, reduction of inflammation, and modulation of cell growth.<sup>4</sup>

## Vitamin K

Vitamin K is another essential fat-soluble vitamin that also has two distinct forms. Vitamin K<sub>1</sub> (phylloquinone) is mainly found in green leafy vegetables and some vegetable oils.<sup>2,7</sup> It is the primary dietary source of vitamin K in the United States, whereas K<sub>2</sub> (menaquinones [MKs]; e.g., MK-7 and MK-4) is found in butter, egg yolks, some cheeses, fermented dairy products, and is also produced by lactic acid bacteria in the intestine.<sup>2,7</sup> Both vitamin K forms are deemed essential cofactors for the production of proteins that are involved in the homeostasis of calcium and blood coagulation.<sup>2</sup>

## Functions of vitamin K

**Vitamin K<sub>1</sub>:** Transported to the liver and regulates cofactors that aid in coagulation of the blood.<sup>2</sup>

**Vitamin K<sub>2</sub>:** A cofactor for carboxylase activity, it facilitates the gamma-carboxylation of bone-specific proteins such as osteocalcin (OC) and matrix Gla (MGP).<sup>2</sup> OC takes calcium from the blood and binds it to the bone matrix, which in turn helps increase bone formation.<sup>7</sup> MGP inhibits vascular and soft tissue calcification.<sup>2</sup>

During vitamin K deficiency or insufficiency, osteocalcin and MGP remain uncarboxylated, which is associated with lower bone mineral density (BMD) and an increased risk of osteoporosis and cardiovascular disease.<sup>8</sup>

## Common micronutrient shortfalls

According to nationally representative data, vitamins D and K represent common, significant nutrient gaps for the majority of Americans  $\geq$  2 years of age.<sup>9</sup>

## Proposed synergy between vitamins D and K: bone and cardiovascular health<sup>3</sup>

- Animal and human studies have demonstrated that vitamin D helps stimulate the production of vitamin K-dependent proteins, OC and MGP, which support bone mineralization and decrease vascular calcification.
- Long-term supplementation of vitamin D can lead to increased production of vitamin K-dependent proteins. If the increased demand is not adequately supported through diet or supplementation, the proteins can remain uncarboxylated, which can lead to increased vascular calcification and lower BMD.
- Excess supplemental calcium intake without the support of vitamins D and K can lead to increased calcium deposits in the vascular tissue instead of the bones.

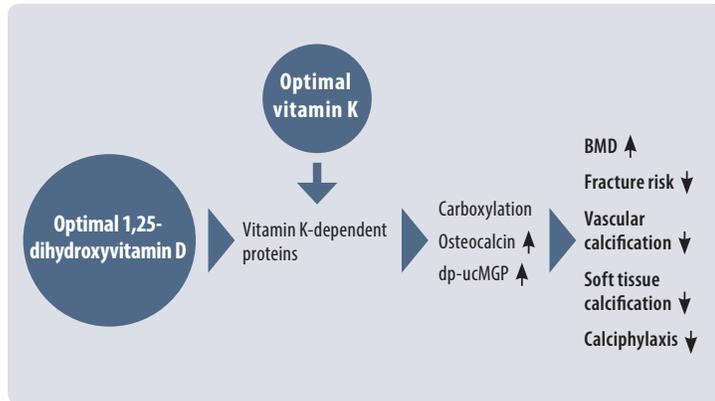


Image adapted from: van Ballegooijen AJ et al. *Int J Endocrinol.* 2017;2017:7454376.

## Research

### Bone health<sup>10</sup>

A randomized controlled trial involving 78 post-menopausal women aged 60-plus was conducted to assess the effects of vitamins D and K on BMD and undercarboxylated OC (UcOC) over a six-month period; 45 women completed the study.

The vitamin K group (n=40) received 15 mg of K<sub>2</sub> TID after every meal, 400 IU calcitriol once daily, and 315 mg calcium carbonate BID. The control group (n=38) received 400 IU calcitriol once daily and 315 mg calcium carbonate BID.

**Results:** There was a statistically significant (P=0.049) increase in lumbar spine (L3) BMD in the vitamin K group compared to the control group. In addition, compared to baseline, the vitamin K group significantly decreased UcOC concentration (P≤0.01). Osteocalcin also non-significantly increased in the vitamin K group. Some observational and animal studies also support these findings.<sup>3</sup>

There were some limitations to the study, which included the small number of participants, high dropout rate, and the absence of a separate comparator group that did not receive any supplementation.

### Cardiovascular health<sup>11</sup>

In a study with 42 patients with chronic kidney disease (CKD) stages 3-5 (non-dialyzed), the researchers assessed the effect of vitamin K<sub>2</sub> substitution on the progression of atherosclerosis and calcification for nine months. The vitamins K+D group received 90 mcg of K<sub>2</sub> with 10 mcg (400 IU) of vitamin D<sub>3</sub>. The vitamin D alone group received 400 IU of vitamin D<sub>3</sub>.

The common carotid intima-media thickness (CCA-IMT), coronary artery calcification score (CACS), uncarboxylated MGP, and osteocalcin levels were measured. They found the thickness of the CCA-IMT along with CACS were significantly lower in the vitamins K+D group compared to the vitamin D only group. The uncarboxylated MGP and OC levels also significantly decreased in the K+D group.

### Additional health benefits

Researchers are also studying the impact of joint supplementation of vitamins D and K on glucose metabolism and inflammation. These studies have found beneficial effects on markers of oxidative stress, upregulation of insulin receptor genes, and enhancement of β-cell proliferation.<sup>3</sup>

#### References:

1. Kullie T et al Vitamin D: An evidence-based review. *J Am Board Fam Med.* 2009;22(6):698-706.
2. Schwalfenberg GK. Vitamins K1 and K2: The emerging group of vitamins required for human health. *J Nutr Metab.* 2017;6254836.
3. van Ballegooijen AJ et al. The synergistic interplay between vitamins D and K for bone and cardiovascular health: A narrative review. *Int J Endocrinol.* 2017;2017:7454376.
4. Nair R et al. Vitamin D: The "sunshine" vitamin. *J Pharmacol Pharmacother.* 2012;3(2):118-126.
5. Vitamin D. Linus Pauling Institute. <https://lpi.oregonstate.edu/mic/vitamins/vitamin-D>. Accessed July 25, 2018.
6. Vitamin D. National Institutes of Health. <https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/>. Accessed July 25, 2018.
7. Maresz K. Proper calcium use: Vitamin K2 as a promoter of bone and cardiovascular health. *Integr Med.* 2015;14(1):34-39.
8. Lanham-New SA. Importance of calcium, vitamin D and vitamin K for osteoporosis prevention and treatment. *Proc Nutr Soc.* 2008;67(2):163-176.
9. Fulgoni VL 3rd et al. Foods, fortificants, and supplements: Where do Americans get their nutrients? *J Nutr.* 2011;141(10):1847-1854.
10. Je SH et al. Vitamin K supplement along with vitamin D and calcium reduced serum concentration of undercarboxylated osteocalcin while increasing bone mineral density in Korean postmenopausal women over sixty years old. *J Korean Med Sci.* 2011;26(8):1093-1098.
11. Kurnatowska I et al. Effect of vitamin K2 on progression of atherosclerosis and vascular calcification in nondialyzed patients with chronic kidney disease stages 3-5. *Pol Arch Med Wewn.* 2015;125(9):631-640.

