Science Review: Vitamins D and K

Research Highlights

- ✓ Vitamin D is important for calcium homeostasis, bone mineralization, and promoting immune and cardiovascular function.[1]
- ✓ Vitamin K is important in blood coagulation, and plays a central role in decreasing calcium accumulation in the smooth muscles of vascular walls.[2]
- ✓ 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.[3]

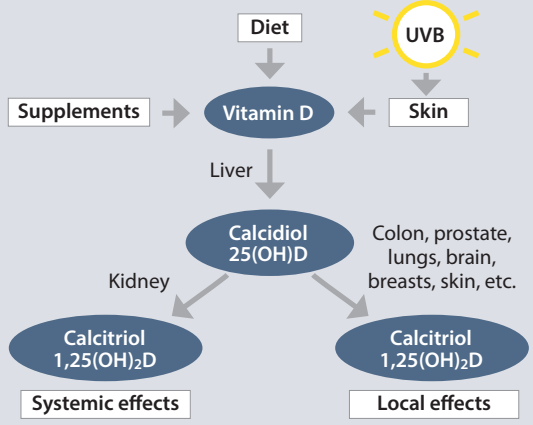
Vitamin D

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.[1]

There are two forms of vitamin D: D_2 (ergocalciferol) obtained from plants, mushrooms, and yeast; and D_3 (cholecalciferol) obtained from animal products such as fatty fish, fish liver oil, egg yolk, and beef liver.[4]

Vitamin D obtained from food, supplements, or sunlight is considered a preprohormone 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.[1,4-6] 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-α-hydroxylase to form 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), or calcitriol, its active form.[1,4-6] 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.[5,6] 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.[5,6] 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.[4]

Vitamin K

Vitamin K is another essential fat-soluble vitamin that also has two distinct forms. Vitamin K_1 (phylloquinone) is mainly found in green leafy vegetables and some vegetable oils.[2,7] It is the primary dietary source of vitamin K in the United States, whereas K_2 (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.[2,7] Both vitamin K forms are deemed essential cofactors for the production of proteins that are involved in the homeostasis of calcium and blood coagulation.[2]

Functions of vitamin K

Vitamin K_1: Transported to the liver and regulates cofactors that aid in coagulation of the blood.[2]

Vitamin K_2: A cofactor for carboxylase activity, it facilitates the gamma-carboxylation of bone-specific proteins such as osteocalcin (OC) and matrix Gla (MGP).[2] OC takes calcium from the blood and binds it to the bone matrix, which in turn helps increase bone formation.[7] MGP inhibits vascular and soft tissue calcification.[2]

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.[8]

Common micronutrient shortfalls

According to nationally representative data, vitamins D and K represent common, significant nutrient gaps for the majority of Americans ≥ 2 years of age.[9]

Proposed synergy between vitamins D and K: bone and cardiovascular health[3]

- 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.

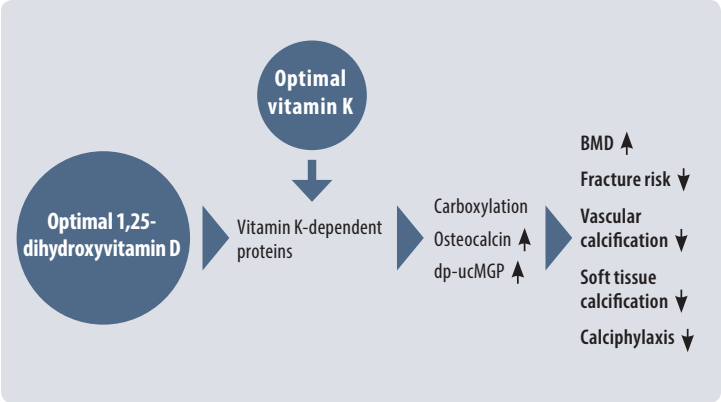


Image adapted from: van Ballegooijen AJ et al. *Int J Endocrinol*. 2017;2017:7454376.

Research

Bone health[10]

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_2 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.[3]

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[11]

In a study with 42 patients with chronic kidney disease (CKD) stages 3-5 (non-dialyzed), the researchers assessed the effect of vitamin K_2 substitution on the progression of atherosclerosis and calcification for nine months. The vitamins K+D group received 90 mcg of K_2 with 10 mcg (400 IU) of vitamin D_3. The vitamin D alone group received 400 IU of vitamin D_3.

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.[3]

References:

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