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vitamk7™

NATURAL VITAMIN K2 AS MK7

General Monograph

OVERVIEW

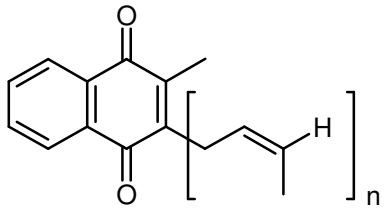
Vitamin K is a generic term for a group of substances which contain the 2-methyl-1,4-naphthoquinone ring structure and which possess hemostatic activity. Substances with Vitamin K activity were originally identified in green leafy vegetables, hemp seeds, liver and fish meal. These substances were found to have antihemorrhagic activity and their collective name was derived form koagulation, the German word for clotting.
In addition to its essential role in hemostasis, Vitamin K is involved in bone metabolism, among other processes.

Vitamin K exists in the following active forms:

VITAMIN K1 produced in plants, fat-soluble and scientifically known as phylloquinone or phytomenadione,
VITAMIN K2 produced in animals, fat-soluble and scientifically known as menaquinone,
VITAMIN K3 synthetically produced, water-soluble and scientifically known as menadione.

The nutritional supplement forms of Vitamin K are Vitamin K1 and Vitamin K2.

VITAMIN K2 is the collective term for a group of Vitamin K compound called menaquinones.
The group chemical name is 2-methyl-3-all-*trans*-polyprenyl-1,4- naphthoquinones.
Menaquinones are designated by the name menaquinone followed by a number, which refers to the number of the isoprene units comprising the side chain and located at position 3 of the naphthoquinone ring.



Specifically, menquinone-7 (MK-7) possesses seven isoprene units in the side chain.

Vitamin K2 is found in chicken egg yolk, butter, cow liver, certain cheese and fermented soybean products such as *natto*.

This form of Vitamin K is also produced by certain bacteria, including some of the bacteria that comprise the microflora of the intestine.
The dietary contribution of Vitamin K2 is much less than that of Vitamin K1 (green leafy vegetables and vegetables oils) and the amount of Vitamin K2 contributed to the body by the intestinal microflora remains unclear.
The fermented soybean product *natto* is rich in MK-7.

ABSORPTION, METABOLISM & EXCRETION

Vitamin K, mainly in the form of Vitamin K1, is principally absorbed from the jejunum and ileum. The efficiency of the absorption is variable and ranges from 10% to 80%. Vitamin K is delivered to the enterocytes in micelles formed from bile salts and other substances. Vitamin K is secreted by enterocytes into the lymphatics in the form of chylomicrons. It enters the circulation via the thoracic duct and is carried in the circulation to various tissues icluding hepatic, bone and spleen, in the form of chylomicron remnants.
In the liver some Vitamin K is stored, some is oxidized to inactive end-products and some secreted with VLDL (very low-density lipoprotein). Approximately 50% of vitamin K is carried in the plasma in the form of VLDL, about 25% in the form of LDL (low-density lipoprotein) and about 25% in the form of HDL (high-density lipoprotein).
Vitamin K undergoes some oxidative metabolism. Excretion of Vitamin K and its metabolites is mainly via the feces. Some urinary excretion of Vitamin K also occurs.

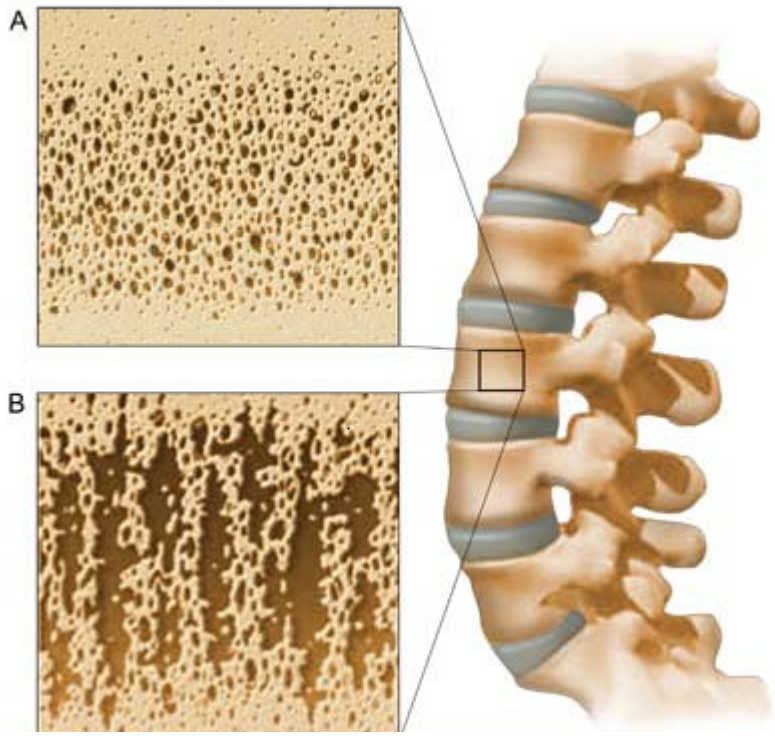
ACTIONS & BENEFITS

➢ *Introduction*

For many years it was thought that vitamin K function was exclusively linked to blood coagulation. However, the past decade vitamin K has been linked also to two of the most important health issues, osteoporosis and cardiovascular disease. This link specifically focuses on calcium utilization - implying that there is concurrent arterial calcification and osteoporosis when metabolism of calcium is inadequate. This is called the ***Calcium Paradox*** [1].
To understand this paradox, one needs to know about the Vitamin K dependent proteins the Gla proteins- specifically Osteocalcin and Matrix Gla Protein [2].
Basic research and clinical studies along with epidemiological knowledge have led to the understanding of circulating Vitamin K for activation of these proteins; involvement of the proteins in the diseases, and which molecular form of vitamin K that offers the optimal solution for supplying K vitamin.

Vitamin K2 has been shown in laboratory experiments, population based studies and clinical trials to be much more effective than K1 in preventing bone loss, reducing fracture risk and significantly reducing the incidence of arterial calcification and risk of cardiovascular event.

➢ *Circulating Vitamin K and Osteoporosis*



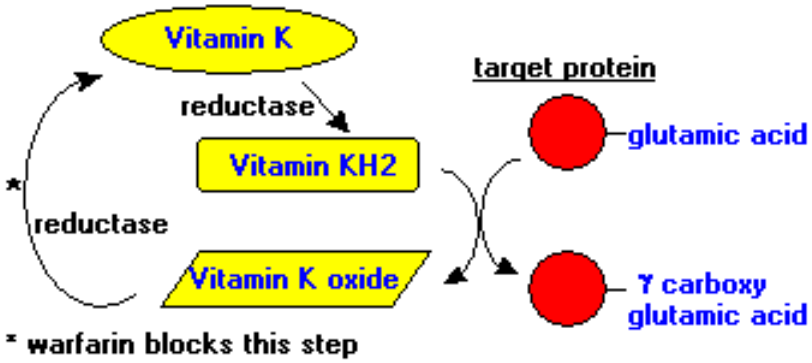
This picture shows how bones become fragile before (A) and in advanced status of osteoporosis (B).

Numerous studies in animals as well as in humans demonstrate correlations between bone disease and low levels of circulating Vitamin K [3,4,5,6]. Low serum levels of Vitamin K strongly influence the secondary modification of osteocalcin - an important protein synthesised by the osteoblastic bone cells. This protein is needed to effectively bind calcium to the bone matrix [7,8,9]. Vitamin K is a cofactor for the enzyme gammaglutamylcarboxylase which modifies the Gla proteins; with optimal Vitamin K levels Osteocalcin is carboxylated and active (cOC); with insufficient levels it is undercarboxylated and inactive (ucOC).

Studies have however shown that supplementation of Vitamin K reduces serum levels of the ineffective form of osteocalcin [10,11,12,13,14]. In addition, a number of human trials have found that regular intake of especially Vitamin K2 reduces the risk of fractures and reduces bone loss [15,16,17,18]. If one questions whether supplementation of Calcium and Vitamin D would do the same as Vitamin K, the answer is no. Large human studies testing Calcium alone, Calcium in combination with Vitamin D, and Calcium plus Vitamin D plus Vitamin K- show that the latter group has shown the best effect on osteoporosis [19,20].
Vitamin K will supplement both these two important substances due to different, yet synergistically, modes of actions of the three.

➢ *Vitamin K2: mechanism of action*

Vitamin K is COFACTOR of vitamin K-dependent carboxylation reactions in a number of biochemical pathways.



The mechanism of the possible anti-osteoporotic activity of Vitamin K is not completely understood. Two Vitamin K-dependent proteins are found in bone: osteocalcin or bone Gla protein (BGP) and the matrix Gla protein (MGP). Osteocalcin appears to be the most abundant non-collagenous protein in the bone. Most of the osteocalcin synthesized by osteoblasts during bone matrix formation is incorporated into bone. This is due to the high specificity of the gamma-carboxyglutamyl residues for the calcium ions of hydroxyapatite. A small amount of osteocalcin is released into the circulation. Osteocalcin appears to act as a regulator of bone mineralization. High levels of circulating undercarboxylated (under-gamma-carboxylated) osteocalcin have been associated with low bone mineral density and increased risk of hip fractures.

The serum level of undercarboxylated osteocalcin may be a more sensitive marker of Vitamin K status than blood coaugulation tests. High levels of undercarboxylated osteocalcin are frequently found in the context of normal blood coaugulation tests.
In vivo and *in vitro* studies have shown that Vitamin K may directly act on bone metabolism. *In vitro* studies have demonstrated that Vitamin K2 inhibits bone resorption by, in part, inhibiting the production of bone resorbing substances such as prostaglandin E2 and interleukin-6.
Vitamin K2 has been reported to enhance human osteoblast-induced mineralization *in vitro* and to inhibit bone loss in steroid-treated rats and ovariectomized rats.

- *Vitamin K and cardiovascular diseases*

Professor Vermeer of VitaK, University of Maastricht, has conducted major studies documenting the inverse correlation between long-term vitamin K intake and atherosclerotic aorta calcification [21,22]. The well known Rotterdam study – including more than 4800 participants - clearly shows that vitamin K2 is much more potent than vitamin K1 in decreasing risk for cardiovascular morbidity and mortality. Like in osteoporosis it has been shown that insufficient Vitamin K2 fails to activate – or carboxylate – an important inhibitor of arterial calcification- Matrix Gla Protein (MGP). Data from humans [23] show that MGP is the strongest inhibitor of soft tissue calcification presently known. The authors have also demonstrated that MGP accumulates mostly around elastin fibers, sites that are prone to get calcium phosphate deposits, and thus needs to be protected more than other parts of the vessel walls. No under-carboxylated MGP could be detected in healthy arteries, while increased amounts of non-functional MGP was found around arterial calcium salt precipitates.

- *Vitamin K: Regress Arterial Calcification? Future Potential.*

Research conducted by Leon Schurgers of VitaK, University of Maastricht, has shown not only an inhibition of induced arterial calcification in the presence of Vitamin K2, but also a regression of preformed calcifications.
Arterial calcification is an important independent risk factor for the development of health concerns including atherosclerosis, myocardial infarction, stroke, and renal disease. It is well established that individuals with marked arterial calcification have an unfavourable prognosis compared to those with no or mild calcification. Therefore, the prevention or reversal of arterial calcification is what researchers and doctors aim for because it may lead to improved outcomes.
The medical community has until recently believed that calcification passively occurred in the end stages of cardiovascular disease. However, in the last ten years it has been discovered that Vitamin K-dependent proteins are directly involved in the inhibition of vascular calcification, and that Vitamin K2 is necessary to activate these proteins.

Induced arterial calcification has been shown to be inhibited completely by Vitamin K2 in vivo [24]. In a study accepted by the journal *Blood*, researchers looked at the potential to regress calcification with vitamin K [25]. Arterial calcification was induced in rats by interfering in the Vitamin K-metabolism, and once calcified, the addition of K1 and K2 were compared to placebo. Linearly, and remarkably, the group receiving a normal dose of K1 continued to calcify comparably to placebo, demonstrating that the normal amount of Vitamin K in the diet had no benefit.
In contrast, high Vitamin K intake not only blocked the progress of further calcium accumulation, but led to an over 37 % reduction of previously accumulated arterial calcium precipitates. It is interesting to note that in the high K1 group, the Vitamin K1 converted into Vitamin K2 to such an extent that tissue concentrations were similar to the K2 supplemented group.
Additionally, the regression of arterial calcification was accompanied by restoration of arterial distensibility, or elasticity, in the high Vitamin K groups to a similar level as in the control animals. These dramatic results support the human consumption studies, i.e. the Rotterdam study, and open an broad new area of research to support the supplementation of vitamin K2 in humans.

CONTRAINDICATIONS, PRECAUTIONS & ADVERSE REACTIONS

➢ *Contraindications*

Vitamin K is contraindicated in those hypersensitive to any component of a Vitamin K-containing product.

➢ *Precautions*

Use of Vitamin K for the treatment of Vitamin K deficiency must be done under medical supervision.

- Vitamin K supplementation and anticoagulation treatment

Patients receiving oral anti-coagulant therapy should not take Vitamin K supplements without consulting their physician first. A group of experts in Europe recently recommended that supplement vitamin K of any kind not exceed 100 µg daily, as this amount is not likely to interact with blood-thinning medications. The recommended dose of 45 µg is well below this threshold, and is a dose that is supported by the literature as efficacious.

- Pregnancy / Breast-feeding

Pregnant women and nursing mothers should avoid supplemental intakes of Vitamin K greater than RDA amounts unless higher amounts are prescribed by their physicians.

➢ *Adverse reaction*

The supplemental forms of Vitamin K, Vitamin K1 and Vitamin K2, are well tolerated.
In one study, doses to 90 µg/day of Vitamin K2 were given for 24 weeks. Few adverse effects were noted. Reversible elevations of some liver tests were noted in a few subjects in the study.

DOSAGE & ADMINISTRATION

There is no typical dosage for Vitamin K.
Some multivitamin preparations contain Vitamin K1 or Vitamin K2 at doses of 25 to 100 µg.

The suggested daily dosage is 45 µg.

Other dosage should be taken under physician's prescription.

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