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A veteran vitamin in versatile role: Vit K

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Abstract

Vitamin K is precisely known for its role in blood clotting. The original term vitamin “K” comes from the K in the Germanic word Koagulation meaning the ability to clot blood or prevent hemorrhage. In recent days, new roles for vitamin K have been emerged in the multifarious fields like, brain health, bone, cardiovascular, hormonal and reproductive health etc. vitamin K deficiency is much more likely to occur in infants but in adults person it is also seen. Symptoms include bruising, hematomas oozing of blood at surgical or puncture sites, stomach pains; risk of massive uncontrolled bleeding; cartilage calcification; and severe malformation of developing bone or deposition of insoluble calcium salts in the walls of arteries. In infants, it can cause some birth defects such as underdeveloped face, nose, bones, and fingers. Vitamin K is changed to its active form in the liver by the enzyme Vitamin K epoxide reductase. Activated vitamin K is then used to gamma carboxylate (and thus activate) certain enzymes involved in coagulation: Factors II, VII, IX, X, and protein C and protein S. Inability to activate the clotting cascade via these factors leads to the bleeding symptoms.

Keywords: Vitamin K, coagulation, calcification, phylloquinone, menaquinones, menadiione

Introduction

The discovery of vitamin K can be traced back to the research of Carl Peter Henrik Dam at the Biochemical Institute of the University of Copenhagen from 1928 to 1930. In his work on cholesterol metabolism, the Danish biochemist observed a spontaneous tendency to hemorrhage in chicks fed for longer than 2 to 3 weeks on cholesterol- and fat-free chicken feed. This coagulation disorder was combined with lowered prothrombin content (Prothrombin D factor II) of the blood [1-3]. At that time, as none of the hitherto known vitamins (e.g. vitamins A, C and D) were capable of preventing the coagulation disorder, Dam postulated a new, fat-soluble vitamin, which regulates coagulation. The latter was apparently present in green vegetables and liver, as supplementary feeding with these nutrients resulted in normal blood coagulation in the animals. Moreover, Dam successfully treated the chickens' hemorrhages with an ether extract obtained from lucerne (alfalfa). Dam Called the antihemorrhagic vitamin “vitamin K” (after “Koagulation:” coagulation) [4]. In the 1930s, several working groups researched the isolation and identification of vitamin K. At this time, a US American research group working with the biochemist Edward Albert Doisy succeeded in isolating the antihemorrhagic vitamin K and elucidating its chemical naphthoquinone ring structure. In 1943, the 2 researchers, Dam und Doisy, were jointly awarded the Nobel Prize for medicine for the discovery and elucidation of the chemical structure of vitamin K [5, 6].

Vitamin K is a name given to a group of fat-soluble vitamins. They are considered essential cofactors in humans for the production of several proteins that are involved in coagulation homeostasis and calcium homeostasis.

Chemically, the vitamin K family comprises 2-methyl-1,4-naphthoquinone (3-) derivatives. Vitamin K includes two natural vitamers: vitamin K₁ and vitamin K₂. Vitamin K₂, in turn, consists of a number of related chemical subtypes, with differing lengths of carbon side chains made of isoprenoid groups of atoms.

Vitamin K₁, also known as phylloquinone, is made by plants, and is found in highest amounts in green leafy vegetables because it is directly involved in photosynthesis. It may be thought of as the plant form of vitamin K. It is active as a vitamin in animals and performs the classic functions of vitamin K, including its activity in the production of blood-clotting proteins. Animals may also convert it to vitamin K₂.

Bacteria in the gut flora can also convert K₁ into vitamin K₂ (Menaquinone). In addition, bacteria typically lengthen the isoprenoid side chain of vitamin K₂ to produce a range of vitamin K₂ forms, most notably the MK-7 to MK-11 homologues of vitamin K₂.

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All forms of K₂ other than MK-4 can only be produced by bacteria, which use these forms in anaerobic respiration. The MK-7 and other bacterially derived forms of vitamin K₂ exhibit vitamin K activity in animals, but MK-7's extra utility over MK-4, if any, is unclear and is a matter of investigation.

Much has been learned about vitamin K₂ and its role in osteoporosis, vascular calcification, osteoarthritis, cancer, and cognition over the past few years. The most commonly known vitamin K types are listed in Table 1, along with their corresponding functions and sources. Deficiency of vitamin K₂ has been linked with vascular calcification and osteoporosis [7]. Matrix GLa protein (MGP) is a vitamin K-dependent protein that inhibits vascular and soft tissue calcification when activated. Vitamin K is also a cofactor for carboxylation of glutamate to gamma carboxyglutamic acid (GLa). GLa containing bone proteins are synthesized by osteoblasts and have been identified as osteocalcin, matrix GLa protein, and pit protein S. Carboxylated osteocalcin (OC) increases after vitamin K₂ administration and there is a connection between uncarboxylated OC and the risk of clinical fractures [8]. Vitamin K₂ (MK-4) supplementation is quite safe and does not induce hypercoagulation even at doses of 15mg three times a day [9].

Biochemical Roles

The only known biochemical role of vitamin K is as a cofactor for the vitamin K-dependent carboxylase that catalyzes the amino acid glutamic acid to g-carboxyglutamic acid (Gla) [10, 11]. This can be achieved by all forms of vitamin K, albeit with different enzyme affinities. This carboxylation reaction is critical to the calcium-binding function of vitamin K-dependent proteins. The degree to which a vitamin K-dependent protein is carboxylated has been used for the assessment of vitamin K nutritional status. As the vitamin K-dependent g-carboxylation is a post-translational event, these carboxylated measures of vitamin K-dependent proteins are

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used as functional indicators of vitamin K status, whereas total concentrations of vitamin K-dependent proteins are influenced by other factors independent of vitamin K. The hepatic vitamin K-dependent proteins involved in coagulation are factors II (prothrombin), VII, IX, and X and proteins C, S, and Z, all of which need vitamin K for physiologic activation. Multiple vitamin K-dependent proteins have been identified in extrahepatic tissues; however, their biologic roles are still being elucidated. Of the extrahepatic proteins, osteocalcin and matrix g-carboxyglutamic acid protein are perhaps the best studied for their role in regulation of calcium binding in bone and soft tissue. All forms of vitamin K share a common naphthoquinone ring but differ in the position-3 side chain (Figure 1). Phylloquinone contains the phytyl group as its side chain, whereas the menaquinones contain a polyisoprenoid side chain of varying lengths at position-3 of the naphthoquinone ring. The phytyl side chain of phylloquinone is thought to be removed to form menaquinone-4. Even though menaquinone-4 is not abundant in the food supply, it is found in high concentrations in certain tissues. This has led to the hypothesis that menaquinone-4 can have unique roles in novel functions of vitamin K, independent of its role as an enzyme cofactor. These include prevention of oxidative injury to oligodendrocytes in the brain [12], acting as a ligand for a xenobiotic receptor in bone cells [13], playing a role in gene expression in osteoblasts [14], and modulation of inflammatory responses [15].

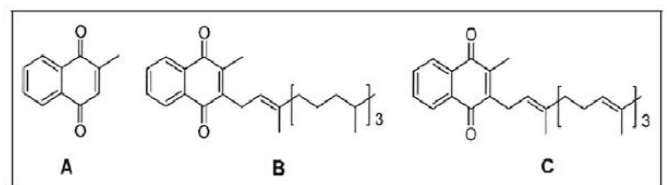


Fig 1: Chemical structures of vitamin K. **A.** Menadione; **B.** Phylloquinone; **C.** Menaquinone-4

Table 1: Food sources of vitamins K1 and K2

Vitamin K1	Vitamin K2
(1) Boiled spinach	(1) Nattō (fermented soy)
(2) Cooked broccoli	(2) Hard cheese (Gouda)
(3) Coleslaw with homemade dressing	(3) Soft cheese (blue cheese)
(4) Cooked asparagus	(4) Egg yolk
(5) Soybean oil	(5) Butter
(6) Red or green grapes	(6) Chicken liver
(7) Plums	(7) Salami
(8) Kidney beans	(8) Chicken breast
(9) Yogurt	(9) Ground beef
(10) Mayonnaise	(10) Sauerkraut
(11) Margarine	(11) Fermented milk (kefir)

Source. USDA National Agricultural Library, Composition Vitamins and Minerals. Kamao M, S., et al, Vitamin K Content of Foods and Dietary Vitamin K Intake in Japanese Young Women. J Nutr Sci Vitaminol (Tokyo), 2007. 53: p. 464-470.

Vitamin K Deficiency

The daily recommended requirement for vitamin K is 90 $\mu\text{g}/\text{day}$ for women and 120 $\mu\text{g}/\text{day}$ for men¹⁶. Sources of vitamins K1 and K2 are listed in Table 1. Deficiency based on bleeding problems is rare, except in newborns. Prior to the use of prophylactic vitamin K injections in neonates, deficiency of vitamin K would result in a hemorrhagic condition with associated cutaneous, intrathoracic, gastrointestinal, and intracranial bleeding. A more sensitive indicator of vitamin K deficiency would be a measure of uncarboxylated osteocalcin or uncarboxylated GLa proteins. Undercarboxylated osteocalcin is considered a marker for hip fracture risk¹⁷. This may be more relevant now that we understand the function of vitamin K2 in the vascular system and bone health. There are a number of conditions and medications that interfere with vitamin K absorption, which are listed as follows:

Vitamin K Interactions and Vitamin K Absorption

- i) Antibiotic use (longer than 10 days)
- ii) Dilantin (use in pregnancy or nursing may deplete vitamin K in newborns)
- iii) Low fat diet and fat blocking supplements
- iv) Bile acid sequestrants (which prevent fat absorption) such as cholestyramine, colestipol, or colesevelam
- v) Orlistat, Xenical, and Olestra (FDA requires addition of vitamins K,AE, and D to food products containing Olestra)
- vi) Mineral oil
- vii) Preservative butylated hydroxytoluene (BHT)
- viii) GI tract diseases, liver diseases, and estrogen drugs

Effect of Vitamin K on the Bones and Vascular System

As a result of vitamin K-mediated γ -carboxylation, the various GLa proteins can bind calcium ions and are activated in this way. Carboxylated osteocalcin (cOC) binds calcium in the bone tissue, which is incorporated into the hydroxyapatite of the bone with the help of the osteoblasts. A low dietary vitamin K intake and high proportion of uncarboxylated osteocalcin (ucOC) are independent risk factors for hip fractures¹⁸⁻²¹. The production and activation of osteocalcin (OC) is regulated by vitamin K and 1,25-dihydroxyvitamin D [1,25(OH)₂D; calcitriol]^{21, 22}. 1,25(OH)₂D promotes the transcription of the osteocalcin gene, whereas vitamin K promotes the posttranscriptional carboxylation of Gla residues in the osteocalcin propeptide^{22, 23}. Furthermore it was demonstrated that 1,25(OH)₂D enhances the activity of γ -glutamyl carboxylase, suggesting that the carboxylation of osteocalcin is stimulated by vitamin D and that menaquinone-4 stimulates 1,25-dihydroxyvitamin D₃-induced mineralization by human osteoblasts²⁴. There is growing evidence about the synergistic effect on bone health of vitamin K and vitamin D. But further data is required in order to have a complete understanding of the complex interaction between vitamin K, vitamin D and bone metabolism. Whereas carboxylated osteocalcin (cOC) promotes the incorporation of calcium into the bone matrix, thus supporting bone metabolism, the vitamin K-dependent matrix Gla protein (cMGP) counteracts vascular calcification and age-related wear and tear on the arteries and protects the blood vessels from calcium overload (Fig. 2)^{25, 26}.

Bone health

In the Nurses' Health Study, which investigated 72,327

women aged from 38–63 years, the effect of daily vitamin K intake on bone fragility was investigated over a 10-year period. It was shown that women with a daily vitamin K intake of ≥ 109 mg had a 30% reduction in the risk of hip fracture compared to women with an intake of <109 mg (RR: 0.70; 95% CI: 0.53, 0.93)¹⁹. In a double-blind, placebo-controlled study with 55 adolescents, the proportion of uncarboxylated osteocalcin (ucOC) was significantly reduced compared to placebo by a daily supplement of 45 mg vitamin K2 as menaquinone-7 and the proportion of carboxylated osteocalcin (cOC) was increased, indicating improved bone mineralization²⁷. A meta-analysis of 13 randomized controlled studies investigated the effect of vitamin K supplementation as vitamin K1 (1–10 mg daily) or vitamin K2 (15–45 mg MK-4 daily) on the fracture rate and bone density. It was shown that, compared with placebo, particularly vitamin K2 as MK-4 reduces the risk of vertebral fractures by 60% (OR: 0.40; 95% CI, 0.25–0.65), of hip fractures by 77% (OR: 0.23; (95% CI, 0.12–0.47) and of non-vertebral fractures by 81% (OR: 0.19; 95% CI, 0.15–0.35)²⁸. In a recent 3-year placebo-controlled study in 244 healthy postmenopausal women, a daily supplement of 180 mg vitamin K2 as MK-7 led to a significant improvement in bone density, bone health and bone strength. The quotient of ucOC/cOC served as a marker for the vitamin K status and was considerably improved by MK-7²⁹. In a randomized study in 241 postmenopausal women, a supplement of 45 mg vitamin K2 (MK-4, menaquinone-4) over a period of 24 months led to a significant rise in carboxylated osteocalcin (cOC) and a significantly reduced fracture rate compared with the control group.

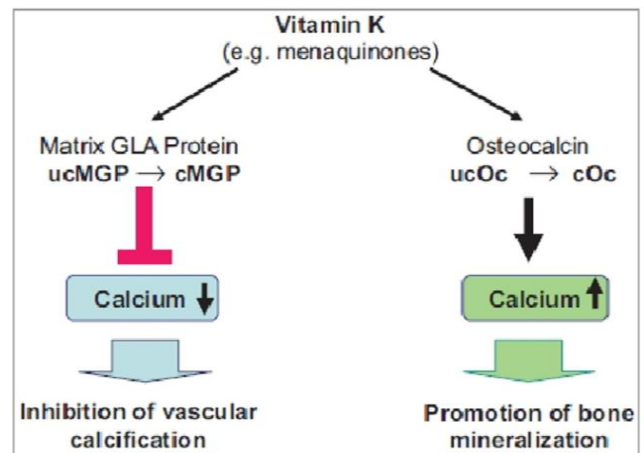


Fig 2: Effect of vitamin K on bone and vascular health

Vascular health

In the Rotterdam Study, a large-scale, population-based study with 4,807 Dutch women and men (age: 55C), the effect of dietary vitamin K1 and vitamin K2 over a 10-year period (1990 to 2000) was investigated with regard to the risk of coronary heart disease, arterial calcification and overall mortality. This study found that vitamin K1 (intake: ≥ 250 mg/day) had no protective effect on the cardiovascular system or overall mortality. Vitamin K2 (intake: ≥ 25 mg/day) reduced the relative risk of dying of heart disease by 57%. Vitamin K2 also markedly reduced the occurrence of coronary heart disease (by 41%) and overall mortality (by 36%). Vitamin K2 even reduced the risk of severe arterial calcification by 52% (OR: 0.48)³⁰.

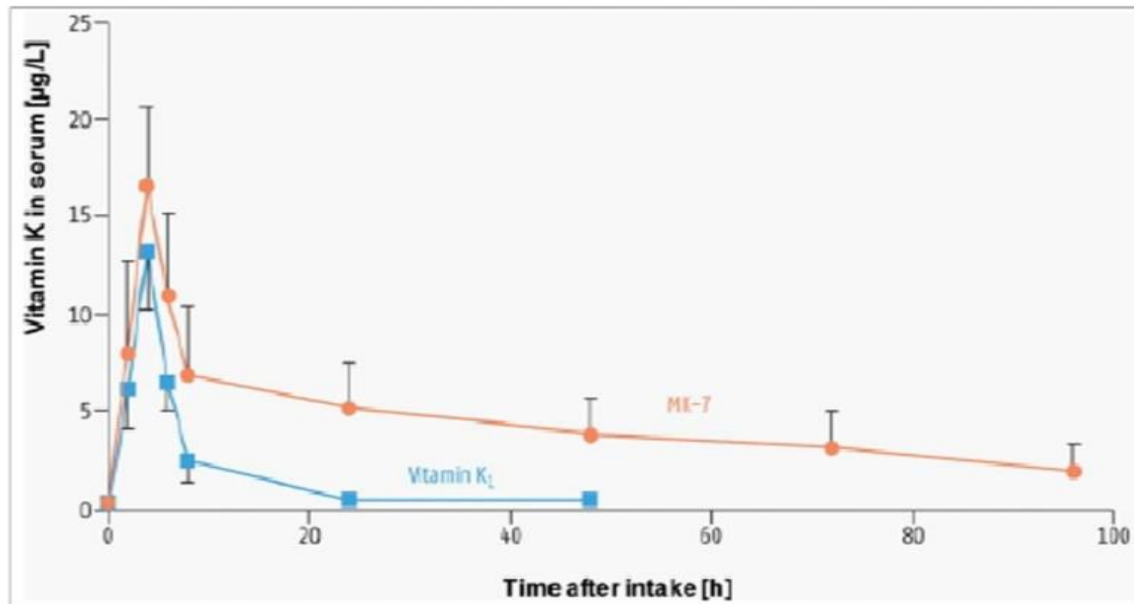


Fig 3: Comparison of oral bioavailability of vitamin k1 and MK-7: Vitamin K serum levels following a single dose of 1 mg Vitamin K1 or 1 mg MK-7^[49]

Vitamin K and Reproductive Endocrinology

It has been reported in rodent studies that the vitamin K concentrations in ovaries are higher than in other organs^[31]. Furthermore, the most abundant form of vitamin K measured in reproductive organs is menaquinone-4, suggestive of a role for vitamin K in female reproduction that is independent of γ -carboxylation. However, to date there are no reports of vitamin K linked to reproductive functions. In China, vitamin K acupuncture point injection has been a standard treatment for dysmenorrhea since the 1980s^[32]. Dysmenorrhea is a common gynecologic complaint and has been reported to be one of the most common causes of periodic absenteeism from school or work in young women^[33].

Vitamin K and Insulin Sensitivity

In a 3-year randomised, double-blind, controlled trial of 355 patients, vitamin K significantly improved insulin sensitivity in men with diabetes. Vitamin K is involved in pancreatic β -cell proliferation, insulin sensitivity, production of adiponectin and increased glucose tolerance, all of which may have contributed to these results. As a vitamin K inhibitor, warfarin may potentially negate these effects. In summary, vitamin K may improve insulin sensitivity in men with diabetes^[34].

Vitamin K and Cancer

Much research is taking place presently looking at the vitamin K family and its potential anticancer effect^[35]. Vitamin K₂ may safely suppress growth and invasion of human hepatocellular carcinoma via protein kinase A activation and result in moderate suppression of tumor recurrence^[36]. It has also been shown to result in growth suppression in a dose dependent manner in lung cancer cells in vitro^[37]. Similar results were found in pancreatic cancer cells^[38]. A cohort study (LOE = B) of over 11,000 patients showed that higher vitamin K₂ intake was associated with a significant reduction in advanced prostate cancer in particular^[39]. There was no association with higher vitamin K₁ intake and reduction of prostate cancer.

Vitamin K₂ has been shown to inhibit the growth of human cancer cell lines, including hepatoma lines, as well as to treat

myelodysplastic syndrome^[40-43]. Two trials seem to indicate that vitamin K₂ 45 mg/day reduces the development of hepatocellular carcinoma (HCC) in patients with liver cirrhosis and that vitamin K₂ significantly reduces the recurrence of HCC in patients following the curative treatment of HCC with an associated reduction in all-cause mortality in these patients^[44-51].

Vitamin K and Haemodialysis

Pilkey et al^[52] demonstrated that 29% of patients with haemodialysis have coexisting subclinical vitamin K deficiency.

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