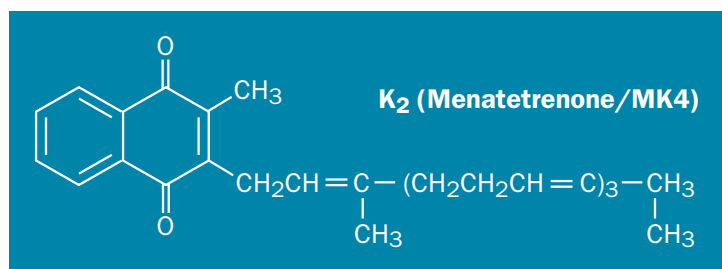


Vitamin K2



Introduction

Vitamin K is a fat-soluble vitamin essential for the functioning of several proteins involved in blood clotting.¹ Discovered in 1929 by Danish scientist Henrik Dam, the vitamin received the letter “K” because the initial discoveries were reported in a German journal in which the substance was designated as “Koagulationsvitamin.” Research during the last 30 years has resulted in greater appreciation for vitamin K. For instance, although vitamin K is usually identified as a critical factor in blood coagulation, recent research reveals it is a cofactor in bone metabolism.²⁻⁸ Inhibition of cancerous cell growth *in vivo* and *in vitro* by vitamin K has also been observed.⁹⁻¹⁶ Furthermore, recent findings suggest it may be an important cofactor in the treatment and prevention of atherosclerosis and calcified arterial plaque.^{17,18} The primary dietary source of vitamin K is generally green leafy vegetables. Consequently, high vitamin K intake may serve as a marker for a healthy diet rich in vegetables.¹⁹

Biochemistry

Vitamin K2 is part of a family of structurally similar fat-soluble, 2-methyl-1,4-naphthoquinones that include phyloquinone (K1), menaquinones (K2), and menadiione (K3). The members of the vitamin K family possess an identical naphthoquinone skeleton with various side chains that distinguish them. The best-known member of the vitamin K family is phyloquinone, also known as phytonadione or menaphthone, so named because of its intimate relationship with photosynthesis in plant leaves. Phyloquinone is found in many higher plants as well as algae, with the highest concentrations found in green leafy vegetables.²⁰

Menaquinones also occur naturally, but are not produced by plants; rather, they are produced by a vast array of bacteria. Menaquinones were originally isolated from putrefied fishmeal as a product of microbial synthesis.²¹ Recent studies have discovered menaquinones can actually be produced by animals and probably humans from the conversion of other forms of vitamin K.^{22,23} The most common form of vitamin K in animals is menaquinone-4 (MK-4), produced by intestinal bacteria from exogenous naphthoquinones and transformed endogenously in our own cells.²⁴

Pharmacokinetics

Vitamin K1 is absorbed from the gastrointestinal tract in the presence of bile salts and pancreatic lipase. Once absorbed, vitamin K accumulates in the liver, spleen, and lungs, but significant amounts are not stored in the body for long periods.

The action of vitamin K1, when administered parenterally, is generally detectable within 1-2 hours, and hemorrhage is usually controlled within 3-8 hours. A normal prothrombin level may often be obtained in 12-14 hours.²⁵

The pharmacokinetics of supplemental vitamin K2 is not yet clearly understood, although its clinical efficacy is evident.

Mechanisms of Action

Vitamin K is a cofactor in a number of biochemical pathways. Those most commonly associated with vitamin K are the vitamin K-dependent carboxylation reactions. In these reactions the reduced form of vitamin K (hydroquinone) de-protonates glutamate via the gamma-glutamyl carboxylase enzyme. The epoxide formed is recycled via vitamin K epoxide reductase and quinone reductase, and glutamic acid-containing proteins, such as coagulation factors II (prothrombin), VII, IX, and X, protein C, and protein S, are carboxylated. Compared to the other vitamin K analogues, vitamin K2 has the most potent gamma-carboxylation activity.²⁶

Vitamin K functions in the post-translational modification of a number of vitamin K-dependent proteins such as osteocalcin, a bone protein containing gamma-carboxyglutamic acid, discovered in 1975.²⁷ Gamma-carboxylation of the glutamic acid in osteocalcin is vitamin K dependent and involves the conversion of glutamic acid residues (Glu) to gamma-carboxyglutamic acid residues (Gla). A number of calcium-binding proteins, such as calbindin and osteocalcin, contain gamma-carboxyglutamate. These proteins are involved with calcium uptake and bone mineralization. Osteocalcin is synthesized in osteoblasts.²⁸ Because osteocalcin that is not carboxylated cannot bind to hydroxyapatite, serum levels of osteocalcin are a good biochemical marker of the metabolic turnover of bone.²⁹

Unlike blood coagulation proteins, which need much lower levels of vitamin K for complete gamma-carboxylation, higher levels of vitamin K are essential for the total gamma-carboxylation of osteocalcin.³⁰ Dietary intake of vitamin K in 219 healthy adults eating an average U.S. diet was found to be insufficient for gamma-carboxylation of osteocalcin, while normal prothrombin time was maintained.³¹ An elevated level of serum glutamic acid under-carboxylated osteocalcin is indicative of vitamin K deficiency and is associated with reduced hip bone mineral density (BMD) and increased fracture risk in healthy elderly women.³² Rats with hypoprothrombinemia were given vitamin K3 or K2 orally (0.1 mg/kg) and absorption and concentration in the liver were compared. The most potent form was found to be vitamin K2.³³

Vitamin K2, in the form of menaquinone-4, is the most biologically active form of vitamin K, up-regulating the gene expression of bone markers. MK-4 has been clinically used in the treatment of osteoporosis in Japan, where extensive research in this field has been taking place. This research confirms that MK-4 is converted from dietary vitamin K1 and then accumulates in various tissues at high concentrations, although the pathway by which MK-4 is converted remains unclear.³⁴

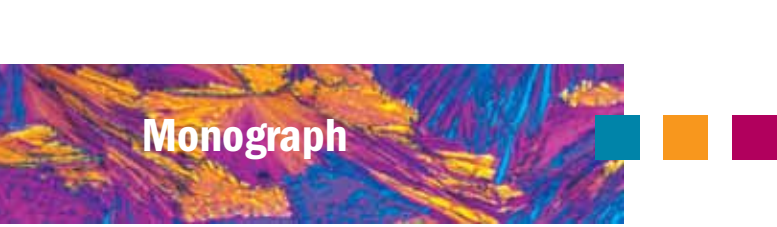
Deficiency States and Symptoms

Deficiency of vitamin K is associated with impaired blood clotting, demonstrated by such symptoms as easy bruising, frequent nosebleeds, bleeding gums, heavy menstrual periods, and presence of blood in the urine and/or stool. Vitamin K deficiency may be demonstrated through laboratory measurement of blood clotting time. Individuals at greatest risk for vitamin K deficiency include those taking vitamin K antagonist anticoagulant drugs, those with significant liver impairment, and those who suffer from fat malabsorption conditions.^{35,36} Vitamin K deficiency in a newborn is serious, as it may result in a bleeding disorder called vitamin K deficiency bleeding (VKDB). VKDB is life-threatening, but it can be easily prevented by administering an injection of vitamin K to newborns, a practice recommended by the American Academy of Pediatrics and a number of similar international organizations.³⁷

Clinical Indications

Osteoporosis

Several human trials have found vitamin K2 effective in the treatment of osteoporosis.^{26,38-41} In a randomized, open-label study, 241 osteoporotic women were given either 45 mg/day vitamin K2 and 150 mg elemental calcium (treatment group; n=120) or 150 mg elemental calcium (control group; n=121). After two years, vitamin K2 was shown to maintain lumbar BMD. Patients receiving vitamin K2 also experienced significantly lower fracture incidence (10% versus 30%, in the treatment and control groups, respectively).⁴¹ In a double-blind, placebo-controlled, 24-week study, 80 patients with osteoporosis received either 90 mg/day vitamin K2 or placebo. Second metacarpal BMD was increased by 2.20 ± 2.48 percent compared to placebo, which decreased by 7.31 ± 3.65 percent.³⁹



Monograph

Vitamin K2 in Osteoporosis of Postmenopausal Women

The incidence of osteoporosis is high in postmenopausal women. A number of trials have demonstrated vitamin K2 induces significant reductions in bone loss in postmenopausal osteoporotic women. In a controlled clinical trial, 172 osteoporotic/osteopenic women ($BMD < 0.98 \text{ g/cm}^2$) were randomly assigned to receive vitamin K2 (45 mg/day), 1-alpha-hydroxycholecalciferol vitamin D3 (a synthetic analog of active vitamin D3) 1 mcg/day, both, or placebo for 24 months. Combination therapy resulted in a significant 4.92 ± 7.89 percent increase in BMD, while vitamin K2 alone resulted in only a 0.135 ± 5.44 percent increase in BMD – higher, but not statistically significantly higher, than baseline values. However, at 18- and 24-month evaluations, BMD was significantly higher in the vitamin K2 group compared to the control group. In this study a combination of vitamins K2 and D3 proved more protective than either supplement alone.²⁶

A longitudinal study of 17 postmenopausal women given vitamin K2 (45 mg/day) for one year found vitamin K2 suppressed the decrease in spinal BMD, with a slight increase ($0.23 \pm 0.47\%$) compared to the control group of 19 postmenopausal women who experienced a decrease ($-2.87 \pm 0.51\%$) in BMD.⁴²

Ninety-two postmenopausal women, ages 55-81, were randomly assigned to one of four groups: vitamin K2 (45 mg/day), 1-alpha-hydroxyvitamin D3 (0.75 mcg/day), a combination of vitamins K and D (same dosage as above), or calcium lactate (2 g/day). The vitamin-K and -D groups experienced significant increases in BMD compared to the calcium group over a two-year period, while the combined treatment was synergistic, significantly increasing lumbar BMD by 1.35 percent.^{43,44}

Vitamin K2 and Bisphosphonates

A number of bisphosphonates (e.g., etidronate, alendronate, and risedronate) are used in the treatment of osteoporosis. These drugs, although generally considered to be more effective than vitamin K2 in increasing BMD, seem to work synergistically with it.

A randomized, open-label study of 98 postmenopausal, osteoporotic women found significantly decreased fracture rates in 23 subjects (2/23) taking

vitamin K2 (45 mg/day) and 25 subjects (2/25) taking etidronate (200 mg/day for two weeks every three months), compared to 24 subjects (6/24) taking calcium lactate (2 g/day). The fracture rate was decreased further in 26 subjects (1/26) taking a combination of vitamin K2 and etidronate.⁴⁵

The bisphosphonate, alendronate (Fosamax®), encourages cortical bone growth by inducing apoptosis of osteoclasts. In a 2004 study, the influence of vitamin K2 on trabecular and cortical bone formation was shown not to interfere with bisphosphonates and the apoptosis of osteoclasts. The authors concluded the combination of vitamin K2 and bisphosphonates could produce an additive effect in osteoporosis prevention.⁴⁶

Vitamin K2 in Osteoporosis of Parkinson's Disease

As a general population the elderly are at high risk for osteoporosis; Parkinson's disease, however, compounds the risk. Research of elderly populations has found a high incidence of hip fractures and osteoporosis in Parkinson's patients,^{47,48} in part related to vitamin D deficiency⁴⁹ and immobilization.⁵⁰ The deficiency does not appear to be related to lack of 25-hydroxyvitamin D3, but rather to suppression of 1,25-dihydroxyvitamin D3 (the active form of vitamin D) by high serum calcium. The application of vitamin K2 significantly increased 1,25-dihydroxyvitamin D3 and decreased serum calcium.⁵⁰ Vitamin K2 (45 mg/day for 12 months) to 54 female osteoporotic Parkinson's patients 65 years or older resulted in one hip fracture, compared to 10 fractures (eight hip, one radius, one ankle) in 54 matched, untreated, osteoporotic Parkinson's patients. Hip fractures were caused by falls and no significant differences were noted in number of falls between groups. The average bone loss in the untreated group was 4.3 ± 2.5 percent of BMD compared to 1.3 ± 0.4 percent in age-matched controls. Vitamin K2-treated patients experienced a 0.9 ± 1.2 percent gain in BMD.⁵⁰

Vitamin K2 in Bone Loss from Leuprolide

A moderate reduction in BMD is one of the frequent side effects of the gonadotropin-releasing hormone antagonist leuprolide for endometriosis, leiomyomas, and prostate cancer.^{51,52} Administration of vitamin K2 (45 mg/day; n=28) or the combination of K2 and 1,25-dihydroxyvitamin D3 (45 mg/day and 0.5 mcg/

day, respectively; $n=28$) resulted in partial prevention of bone loss compared to the leuprolide-only group ($n=28$) or the vitamin D-only group ($n=26$). Bone loss after six months as measured by lumbar spine BMD was 5.25 percent in the leuprolide-only group, 4.13 percent in the vitamin D group, 3.72 percent in the vitamin K group, and 3.59 percent in the group taking vitamins K and D.⁵³

Vitamin K2 in Bone Loss from Prednisolone

Use of glucocorticoids is the most common cause of drug-induced secondary osteoporosis.⁵⁴ Administration of glucocorticoids for long periods of time can lead to a decrease in bone mineral density.⁵⁵ Several studies found vitamin K2 has a marked effect on the loss of BMD in prednisolone-treated patients. Sixty patients with chronic glomerulonephritis were randomized to four groups: control, 1- α -hydroxyvitamin D3 (0.5 mcg/day), vitamin K2 (45 mg/day), or vitamins K2 with D3. Patients concomitantly received prednisolone at a daily dose of 0.7 mg/kg up to a maximum of 40 mg for four weeks, then tapered to 25 mg daily for another four weeks prior to assessment. The control group experienced a significant decrease from baseline in BMD over the eight-week study: -3.19 ± 1.11 percent, compared to the vitamins D, K, and D+K groups that maintained baseline levels (0.28 ± 1.30 , 0.50 ± 1.17 , and 0.44 ± 1.36 percent, respectively).⁵⁶

In a prospective pilot study, 20 children being treated with prednisolone and vitamin D3 (0.03 mcg/kg/day) were continued on D3 plus prednisolone or given that combination plus vitamin K2 (approximately 2 mg/kg/day) for 12 weeks. Vitamins K2 and D3 combined had an additive effect, with a significant increase in lumbar BMD and osteocalcin compared to vitamin D3 alone.⁵⁷

Similar results were obtained in a randomized, prospective, controlled study of 20 patients with glomerulonephritis given 0.8 mg/kg/day prednisolone up to a maximum of 40 mg/day for four weeks, then tapered to 20 mg/day over a six-week period. One group received only prednisolone, while a second group also received vitamin K2 (15 mg three times daily). After 10 weeks, a reduction in lumbar spine BMD (from 1.14 ± 0.12 g/cm² to 1.10 ± 0.11 g/cm²) was noted in the prednisolone-only group. The vitamin K2 group demonstrated a somewhat slower rate of bone loss (from 1.09 ± 0.09 g/cm² to 1.07 ± 0.07 g/cm²).⁵⁵

Vitamin K2 in the Treatment of Bone Loss in Biliary Cirrhosis

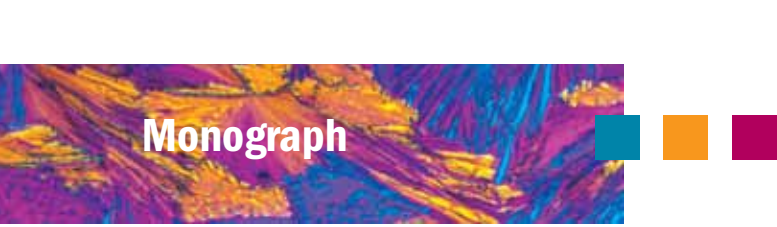
Patients with primary biliary cirrhosis experience osteodystrophy and increased fracture rate and fat malabsorption that can result in deficiencies of vitamins D and K. Serum levels of vitamin K have been found to be low in this population. In a randomized, controlled trial of 27 patients with primary biliary cirrhosis, the treatment group ($n=14$) received vitamin K2 (45 mg/day) for two years. After one year the control group ($n=13$) experienced a 3.5 ± 1.2 percent decrease in BMD, while the vitamin K2 group demonstrated a 0.3 ± 2.3 percent increase in BMD. After two years, the control group demonstrated a 6.9 ± 2.1 percent decrease in BMD, compared to only a 0.8 ± 3.4 percent decrease in the K2 group. BMD was significantly higher in the vitamin K2 group during the two-year period compared to controls.⁵⁸

Vitamin K2 in the Treatment of Osteopenia of Stroke Patients and Skeletal Unloading

Victims of stroke are often immobilized, leading to significant loss of BMD. The most pronounced loss of bone occurs on the hemiplegic side compared to the unaffected side. This loss has been attributed to increased bone resorption, immobilization-induced hypercalcemia, and hypovitaminosis D.⁵⁹ A randomized, controlled trial of 108 hemiplegic stroke victims (54 subjects treated with 45 mg vitamin K2 daily for 12 months and 54 subjects serving as controls) found vitamin K2 effective for preventing disuse bone loss. Second metacarpal BMD on the hemiplegic side increased an average of 4.3 percent with vitamin K2 and decreased an average of 4.7 percent with no treatment. The unaffected side had a 0.9-percent decrease in second metacarpal BMD with vitamin K2 treatment compared to 2.7-percent decrease with no treatment.⁶⁰

Cardiovascular Health

Animal studies have demonstrated vitamin K2, but not vitamin K1, may inhibit the calcification of arterial plaque. A 1996 study on male rats found high-dose vitamin K2 (100 mg/kg body weight daily) inhibited the increase in aortic or kidney calcium induced by megadose synthetic vitamin D2.⁶¹



Monograph

Similarly, a 1997 study was conducted on hypercholesterolemic rabbits placed on a 0.5-percent cholesterol diet. The study demonstrated that administration of high-dose vitamin K2, 1-10 mg/kg body weight daily for 10 weeks, suppressed the progression of atherosclerotic plaques in the aorta and pulmonary arteries. Vitamin K2 was also observed to lower total cholesterol, lipid peroxidation, and factor X activity in plasma, and the ester cholesterol deposition in the aorta compared to the control group.⁶²

Human studies also suggest that dietary vitamin K2 might reduce the risk of cardiovascular disease by reducing coronary calcification. A cross-sectional study of 564 postmenopausal women investigated the association between intake of vitamin K1 and vitamin K2 with coronary calcification. Dietary intake of vitamins K1 and K2 was determined using a food-frequency questionnaire. Of the women sampled, 62 percent (n=360) had coronary calcification. Although vitamin K1 was not associated with any significant effect on coronary calcification (RR=1.17; 95% confidence interval: 0.96-1.42; p(trend)=0.11), it was observed that vitamin K2 intake was associated with the trend toward decreased coronary calcification (RR=0.80; 95%-CI: 0.65-0.98; p(trend)=0.03).¹⁸

Cancer

Both *in vitro* and *in vivo* studies have shown that vitamin K2 exhibits anticancer effects. A number of cancer cell lines have been screened (including liver, colon, leukemia, lung, stomach, lymphocyte, nasopharynx, breast, and oral epidermoid) for inhibition by vitamin K2. Vitamin K2 was found to have an ID₅₀ value from 0.8-2 mM, which, although lower than K1, is still much higher than inhibitory levels of vitamin K3 (18-45 μM).⁵

Other *in vitro* studies have found lower concentrations of menaquinones are effective anticancer agents for a number of cancer cell types. The HOS TE85 human osteosarcoma cell line and the MC3T3-E1 mouse osteoblastic cell line were cultured for three days in a medium containing various concentrations of MK-4. The proliferation of HOS cells was suppressed by vitamin K2 in a dose-dependent manner up to 56 percent of control by 10⁻⁷M of K2, and that of MC3T3-E1 cells was suppressed to 84 percent of control by 10⁻⁶M of vitamin K2.⁶³ MK-3 had an ID₅₀ of 112 μM (112 x 10⁻⁶ M) for the human hepatoma cell line Hep3B.⁶⁴

Vitamin K2 induced growth inhibition via cell cycle arrest and apoptosis in a dose-dependent manner for glioma cells in both rat (C6) and human cell types (RBR17T, T98G).⁶⁵ Incubation with 3 μM of MK-4 for 72 hours decreased cultured leukemic blast cells from 27.6 percent to 17.7 percent. Increasing the concentration of MK-4 to 10 μM decreased blast cell numbers to 3.9 percent.⁶⁶ Vitamin K2 was able to induce cell cycle arrest in the G0G1 transition as well as induce apoptosis in a dose-dependent manner in glioma, hepatoma, and leukemia cell lines.^{65,67,68} Leukemia cell lines resistant to apoptosis still demonstrated induction of differentiation.⁶⁸

Myeloblastic (ML1) and promyelocytic (HL60) cell lines cultured with 1 μM of vitamin K2 showed an 84-percent differentiation induction as measured by nitroterazolum blue staining (NBT), while vitamin K1 showed no differentiation effect. Other differentiation-inducing agents such as retinoic acid, interferon-gamma, and camptothecin were found to have a synergistic effect when combined with vitamin K2.^{69,70} Further studies with isolated leukemia cells (post-myelodysplastic syndrome [MDS] and acute myelocytic leukemia) determined that vitamin K2 at 10 μM was able to selectively induce apoptosis in the leukemia cells in 48 hours.⁷⁰ Three naturally occurring vitamin K2 analogues, MK-3, MK-4, and MK-5, were tested with leukemic blast cells. One of the more potent vitamin K2 analogues tested, MK-4, was found to induce apoptosis in 90 percent of leukemic blast cells. Normal bone marrow cells were also tested with the same concentration of the vitamin K2 analogues for 72 hours. The cytotoxicity to leukemia cells was much more pronounced, while the vitamin K2 analogues had "almost no effect" on normal bone marrow cells.⁶⁸ The selective cytotoxic effect of the three vitamin K2 analogues on immature transformed blasts was confirmed using a more sensitive antibody APO2.7 technique.⁷¹

A number of case studies support the use of vitamin K2 as an anticancer agent. An 80-year-old woman with MDS received an oral dose of 45 mg/day of vitamin K2. After 14 months of treatment her pancytopenia improved and transfusions were no longer needed.⁷² A 72-year-old woman diagnosed with acute promyelocytic leukemia achieved remission when given all-trans-retinoic acid (60 mg/day), enocitabine (200 mg/day), and daunorubicin (40 mg/day) for one week. Relapse

occurred eight months later at which time 20 mg/day of vitamin K2 as MK-4 (route of dose unspecified but assumed to be oral) in conjunction with the previous protocol resulted in the complete disappearance of promyelocytes after two months. Analysis of bone marrow confirmed complete cytogenetic remission.⁷³ A 65-year-old man with MDS who had progressed to acute myeloid leukemia (AML) was treated orally with 90 mg/day of MK-4. Within six weeks he experienced a significant decrease in blast count from 34 to eight percent and increase in platelet count from $31 \times 10^9/L$ to $133 \times 10^9/L$. At 10 months the dosage was reduced to 45 mg/day with an absence of side effects and continuing good performance without myeloablative therapy.⁶⁶

These encouraging results from vitamin K2 therapy have led to a multi-center pilot study in Japan of MDS and post-MDS acute myeloid leukemia (post-MDS AML treatment with vitamin K2 [MK-4]).⁷² In 11 independent institutes, 47 patients received treatment with MK-4. Of 47 patients, 15 had refractory anemia; six had refractory anemia with excessive blast; 11 had refractory anemia with excess of blast and in transformation; three had chronic myelomonocytic leukemia; and 12 had post-MDS AML. MK-4 was effective in reducing blast cell numbers in bone marrow and/or peripheral blood in 71.4 percent (10/14) of those receiving other medications concomitantly. Patients with refractory anemia with excess of blast in transformation, and those with post-MDS AML who used oral vitamin K (MK-4) without other medications, demonstrated 44 percent (4/9) hematological improvement. MK-4 dosage ranged from 20-135 mg/day orally or 10-50 mg/day intravenously, with 83 percent receiving an oral dose of 45 mg/day.⁷⁴

A Japanese trial enlisted 121 patients with hepatocellular carcinoma undergoing conventional therapy consisting of percutaneous tumor ablation and/or transcatheter arterial embolization. Patients were given 45 mg/day oral vitamin K2, which resulted in a significant improvement in survival. Portal vein invasion after 12 months was two percent in the treatment group compared to 23 percent in the control group. At two years, 23 percent in the treatment group, compared to 47 percent in the control group, were found to have invasion into the portal vein.⁷⁵

Drug-Nutrient Interactions

Nutrient Interactions

Animal studies have demonstrated high-dose vitamin A can interfere with vitamin K absorption, although it is not known if this would affect humans in the same manner.^{76,77}

Vitamin E at doses greater than 800 IU may antagonize the effects of vitamin K, potentially increasing the risk of bleeding in individuals on anticoagulation medication or with low vitamin K intake.^{77,78} One study in adults with normal coagulation status found supplementation with 1,000 IU vitamin E for 12 weeks decreased gamma-carboxylation of prothrombin, a vitamin K-dependent protein.⁷⁹

Drug Interactions

High dietary or supplemental vitamin K intake may inhibit the anticoagulant effect of vitamin K antagonists (e.g., warfarin). Generally, it is recommended that individuals on these medications limit vitamin K consumption to amounts typically found in the average diet (90-120 mcg).⁸⁰ Pregnant women on warfarin, anticonvulsants, rifampin, or isoniazid place the newborn at increased risk of vitamin K deficiency as these medications can interfere with fetal vitamin K synthesis.³⁷ Extended use of broad spectrum antibiotics may decrease vitamin K synthesis by intestinal bacteria. Use of cephalosporins and salicylates may adversely affect vitamin K recycling by inhibiting vitamin K epoxide reductase. Furthermore, absorption of vitamin K may be decreased with the use of drugs such as cholestyramine, colestipol, orlistat, and substances such as mineral oil and the fat substitute, olestra.⁸¹

Side Effects and Toxicity

From a large number of clinical trials using dosages in excess of 40 mg/day, there were no reports of side effects associated with any type of hypercoagulable state.^{26,38,39,41} Both animal and clinical studies support the conclusion that vitamin K2 has no abnormal hemostatic activity. In one study, vitamin K2 given to rats at a dose of 250 mg/kg body weight per day for 10 days resulted in no appreciable change in blood coagulation characteristics or platelet aggregation.⁴⁰

Monograph

In a clinical study, 29 elderly, osteoporotic patients were given vitamin K₂ (15 mg three times daily, 30 minutes post-meals) for 12 weeks and monitored for any change in hemostatic balance. After 12 weeks of administration, all hemostatic markers remained within normal range.³⁸ In another study, examining the effect of vitamins K₂ (45 mg/day) and D₃ (1 mcg/day) on BMD in postmenopausal women, hemostatic measures were also examined. Increases in both coagulation and fibrinolysis were noted, but remained within normal range and in balance, with no adverse reactions observed.²⁶

Dosage

There are no established recommended daily allowances (RDAs) for vitamin K₂, although daily adequate intake values have been formed for vitamin K₁ (Table 1).⁷⁷

A typical therapeutic oral dosage for vitamin K₂ for osteoporosis is 45 mg/day.^{26,42-45,50} One study, however, suggested a dosage as low as 1.5 mg/day may provide benefit in maintaining healthy bones in already healthy postmenopausal women.⁸² Therapeutic oral dosages in cancer based on clinical studies range from 20-135 mg/day; however, the most common dosage used has been 45 mg/day.^{66,73-75}

Warnings and Contraindications

It should be noted that the anticoagulant effect of warfarin (Coumadin), functioning by its interference with the clotting effect of vitamin K, can be offset with as little as 1 mg of vitamin K.⁸³ Therefore, use of vitamin K is contraindicated in individuals on anticoagulant therapy.

References

1. Brody T. *Nutritional Biochemistry*. 2nd ed. San Diego, CA: Academic Press; 1999.
2. Rannels SR, Gallaher KJ, Wallin R, Rannels DE. Vitamin K-dependent carboxylation of pulmonary surfactant-associated proteins. *Proc Natl Acad Sci U S A* 1987;84:5952-5956.
3. Shearer MJ. Role of vitamin K and Gla proteins in the pathophysiology of osteoporosis and vascular calcification. *Curr Opin Clin Nutr Metab Care* 2000;3:433-438.

Table 1. Daily Adequate Intakes of Vitamin K₁

Life Stage (Age)	Daily Adequate Intake Values
Infants (0-6 mo)	2.0 mcg
Infants (6-12 mo)	2.5 mcg
Children (1-3 y)	30 mcg
Children (4-8 y)	55 mcg
Children (9-13 y)	60 mcg
Adolescents (14-18 y, including pregnant/nursing females)	75 mcg
Men (≥19 y)	120 mcg
Women (≥19 y, including pregnant/nursing)	90 mcg

4. Suttie JW. Synthesis of vitamin K-dependent proteins. *FASEB J* 1993;7:445-452.
5. Wu FY, Liao WC, Chang HM. Comparison of antitumor activity of vitamins K₁, K₂ and K₃ on human tumor cells by two (MTT and SRB) cell viability assays. *Life Sci* 1993;52:1797-1804.
6. Shiraki M. Vitamin K₂. *Nippon Rinsho* 1998;56:1525-1530. [Article in Japanese]
7. Douglas AS, Robins SP, Hutchison JD, et al. Carboxylation of osteocalcin in post-menopausal osteoporotic women following vitamin K and D supplementation. *Bone* 1995;17:15-20.
8. Schaafsma A, Muskiet FA, Storm H, et al. Vitamin D(3) and vitamin K(1) supplementation of Dutch postmenopausal women with normal and low bone mineral densities: effects on serum 25-hydroxyvitamin D and carboxylated osteocalcin. *Eur J Clin Nutr* 2000;54:626-631.
9. Prasad KN, Edwards-Prasad J, Sakamoto A. Vitamin K₃ (menadione) inhibits the growth of mammalian tumor cells in culture. *Life Sci* 1981;29:1387-1392.
10. Chlebowski RT, Akman SA, Block JB. Vitamin K in the treatment of cancer. *Cancer Treat Rev* 1985;12:49-63.
11. Noto V, Taper HS, Jiang YH, et al. Effects of sodium ascorbate (vitamin C) and 2-methyl-1,4-naphthoquinone (vitamin K₃) treatment on human tumor cell growth *in vitro*. I. Synergism of combined vitamin C and K₃ action. *Cancer* 1989;63:901-906.
12. Ngo EO, Sun TP, Chang JY, et al. Menadione-induced DNA damage in a human tumor cell line. *Biochem Pharmacol* 1991;42:1961-1968.

13. Wu FY, Chang NT, Chen WJ, Juan CC. Vitamin K3-induced cell cycle arrest and apoptotic cell death are accompanied by altered expression of c-fos and c-myc in nasopharyngeal carcinoma cells. *Oncogene* 1993;8:2237-2244.
14. Su WC, Sun TP, Wu FY. The *in vitro* and *in vivo* cytotoxicity of menadione (vitamin K3) against rat transplantable hepatoma induced by 3'-methyl-4-dimethyl- aminoazobenzene. *Gaoxiong Yi Xue Ke Xue Za Zhi* 1991;7:454-459.
15. Gold J. In vivo synergy of vitamin K3 and methotrexate in tumor-bearing animals. *Cancer Treat Rep* 1986;70:1433-1435.
16. Wang Z, Wang M, Finn F, Carr BI. The growth inhibitory effects of vitamins K and their actions on gene expression. *Hepatology* 1995;22:876-882.
17. Geleijnse JM, Vermeer C, Grobbee DE, et al. Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. *J Nutr* 2004;134:3100-3105.
18. Beulens JW, Bots ML, Atsma F, et al. High dietary menaquinone intake is associated with reduced coronary calcification. *Atherosclerosis* 2009;203:489-493.
19. Booth SL, Mayer J. Warfarin use and fracture risk. *Nutr Rev* 2000;58:20-22.
20. Thomson RH. *Naturally Occurring Quinones*. New York, NY: Academic Press; 1971.
21. McKee RW, Binkley SB, MacCorquodale DW, et al. The isolation of vitamins K1 and K2. *J Am Chem Soc* 1939;61:1295.
22. Davidson RT, Foley AL, Engelke JA, Suttie JW. Conversion of dietary phyloquinone to tissue menaquinone-4 in rats is not dependent on gut bacteria. *J Nutr* 1998;128:220-223.
23. Thijssen HH, Drijff-Reijnders MJ. Vitamin K status in human tissues: tissue-specific accumulation of phyloquinone and menaquinone-4. *Br J Nutr* 1996;75:121-127.
24. Seegers WH, Bang NU. *Blood Clotting Enzymology*. New York, NY: Academic Press; 1967.
25. [http://www.rxmed.com/b.main/b2.pharmaceutical/b2.1.monographs/CPS-%20Monographs/CPS-%20\(General%20Monographs-%20V\)/VITAMIN%20K.html](http://www.rxmed.com/b.main/b2.pharmaceutical/b2.1.monographs/CPS-%20Monographs/CPS-%20(General%20Monographs-%20V)/VITAMIN%20K.html) [Accessed August 4, 2009]
26. Ushiroyama T, Ikeda A, Ueki M. Effect of continuous combined therapy with vitamin K(2) and vitamin D(3) on bone mineral density and coagulofibrinolysis function in postmenopausal women. *Maturitas* 2002;41:211-221.
27. Hauschka PV, Lian JB, Gallop PM. Direct identification of the calcium-binding amino acid, gamma-carboxyglutamate, in mineralized tissue. *Proc Natl Acad Sci U S A* 1975;72:3925-3929.
28. Hara K, Akiyama Y, Nakamura T, et al. The inhibitory effect of vitamin K2 (menatetrenone) on bone resorption may be related to its side chain. *Bone* 1995;16:179-184.
29. Price PA, Parthemore JG, Deftos LJ. New biochemical marker for bone metabolism. Measurement by radioimmunoassay of bone GLA protein in the plasma of normal subjects and patients with bone disease. *J Clin Invest* 1980;66:878-883.
30. Booth SL, Suttie JW. Dietary intake and adequacy of vitamin K. *J Nutr* 1998;128:785-788.
31. Binkley NC, Krueger DC, Engelke JA, et al. Vitamin K supplementation reduces serum concentrations of under-gamma-carboxylated osteocalcin in healthy young and elderly adults. *Am J Clin Nutr* 2000;72:1523-1528.
32. Bitensky L, Hart JP, Catterall A, et al. Circulating vitamin K levels in patients with fractures. *J Bone Joint Surg Br* 1988;70:663-664.
33. Akiyama Y, Hara K, Matsumoto A, et al. Comparison of intestinal absorption of vitamin K2 (menaquinone) homologues and their effects on blood coagulation in rats with hypoprothrombinaemia. *Biochem Pharmacol* 1995;49:1801-1807.
34. Suhara Y, Wada A, Okano T. Elucidation of the mechanism producing menaquinone-4 in osteoblastic cells. *Bioorg Med Chem Lett* 2009;19:1054-1057.
35. Olson RE. Vitamin K. In: Shils M, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease*. 9th ed. Baltimore, MD: Williams & Wilkins; 1999:363-380.
36. Ferland G. Vitamin K. In: Bowman BA, Russell RM, eds. *Present Knowledge in Nutrition*. 9th ed. Volume 1. Washington, DC: ILSI Press; 2006:220-230.
37. Thorp JA, Gaston L, Caspers DR, Pal ML. Current concepts and controversies in the use of vitamin K. *Drugs* 1995;49:376-387.
38. Asakura H, Myou S, Ontachi Y, et al. Vitamin K administration to elderly patients with osteoporosis induces no hemostatic activation, even in those with suspected vitamin K deficiency. *Osteoporos Int* 2001;12:996-1000.
39. Orimo H, Shiraki M, Tomita A, et al. Effects of menatetrenone on the bone and calcium metabolism in osteoporosis: a double-blind placebo-controlled study. *J Bone Miner Metab* 1998;16:106-112.
40. Ronden JE, Groenen-van Dooren MM, Hornstra G, Vermeer C. Modulation of arterial thrombosis tendency in rats by vitamin K and its side chains. *Atherosclerosis* 1997;132:61-67.
41. Shiraki M, Shiraki Y, Aoki C, Miura M. Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. *J Bone Miner Res* 2000;15:515-521.

42. Iwamoto I, Kosha S, Noguchi S, et al. A longitudinal study of the effect of vitamin K2 on bone mineral density in postmenopausal women a comparative study with vitamin D3 and estrogen-progestin therapy. *Maturitas* 1999;31:161-164.
43. Iwamoto J, Takeda T, Ichimura S. Effect of combined administration of vitamin D3 and vitamin K2 on bone mineral density of the lumbar spine in postmenopausal women with osteoporosis. *J Orthop Sci* 2000;5:546-551.
44. Iwamoto J, Takeda T, Ichimura S. Treatment with vitamin D3 and/or vitamin K2 for postmenopausal osteoporosis. *Keio J Med* 2003;52:147-150.
45. Iwamoto J, Takeda T, Ichimura S. Combined treatment with vitamin K2 and bisphosphonate in postmenopausal women with osteoporosis. *Yonsei Med J* 2003;44:751-756.
46. Hiruma Y, Nakahama K, Fujita H, Morita I. Vitamin K2 and geranylgeraniol, its side chain component, inhibited osteoclast formation in a different manner. *Biochem Biophys Res Commun* 2004;314:24-30.
47. Johnell O, Melton LJ 3rd, Atkinson EJ, et al. Fracture risk in patients with parkinsonism: a population-based study in Olmsted County, Minnesota. *Age Ageing* 1992;21:32-38.
48. Kao CH, Chen CC, Wang SJ, et al. Bone mineral density in patients with Parkinson's disease measured by dual photon absorptiometry. *Nucl Med Commun* 1994;15:173-177.
49. Sato Y, Kikuyama M, Oizumi K. High prevalence of vitamin D deficiency and reduced bone mass in Parkinson's disease. *Neurology* 1997;49:1273-1278.
50. Sato Y, Honda Y, Kaji M, et al. Amelioration of osteoporosis by menatetrenone in elderly female Parkinson's disease patients with vitamin D deficiency. *Bone* 2002;31:114-118.
51. Smith MR, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2001;345:948-955.
52. Dawson-Hughes B. Bone loss accompanying medical therapies. *N Engl J Med* 2001;345:989-991.
53. Somekawa Y, Chiguguchi M, Harada M, Ishibashi T. Use of vitamin K2 (menatetrenone) and 1,25-dihydroxyvitamin D3 in the prevention of bone loss induced by leuprolide. *J Clin Endocrinol Metab* 1999;84:2700-2704.
54. Rehman Q, Lane NE. Effect of glucocorticoids on bone density. *Med Pediatr Oncol* 2003;41:212-216.
55. Yonemura K, Kimura M, Miyaji T, Hishida A. Short-term effect of vitamin K administration on prednisolone-induced loss of bone mineral density in patients with chronic glomerulonephritis. *Calcif Tissue Int* 2000;66:123-128.
56. Yonemura K, Fukasawa H, Fujigaki Y, Hishida A. Protective effect of vitamins K2 and D3 on prednisolone-induced loss of bone mineral density in the lumbar spine. *Am J Kidney Dis* 2004;43:53-60.
57. Inoue T, Sugiyama T, Matsubara T, et al. Inverse correlation between the changes of lumbar bone mineral density and serum undercarboxylated osteocalcin after vitamin K2 (menatetrenone) treatment in children treated with glucocorticoid and alfacalcidol. *Endocr J* 2001;48:11-18.
58. Nishiguchi S, Shimoi S, Kurooka H, et al. Randomized pilot trial of vitamin K2 for bone loss in patients with primary biliary cirrhosis. *J Hepatol* 2001;35:543-545.
59. Sato Y, Kuno H, Kaji M, et al. Increased bone resorption during the first year after stroke. *Stroke* 1998;29:1373-1377.
60. Sato Y, Honda Y, Kuno H, Oizumi K. Menatetrenone ameliorates osteopenia in disuse-affected limbs of vitamin D- and K-deficient stroke patients. *Bone* 1998;23:291-296.
61. Seyama Y, Horiuchi M, Hayashi M, Kanke Y. Effect of vitamin K2 on experimental calcinosis induced by vitamin D2 in rat soft tissue. *Int J Vitam Nutr Res* 1996;66:36-38.
62. Kawashima H, Nakajima Y, Matubara Y, et al. Effects of vitamin K2 (menatetrenone) on atherosclerosis and blood coagulation in hypercholesterolemic rabbits. *Jpn J Pharmacol* 1997;75:135-143.
63. Akedo Y, Hosoi T, Inoue S, et al. Vitamin K2 modulates proliferation and function of osteoblastic cells in vitro. *Biochem Biophys Res Commun* 1992;187:814-820.
64. Nishikawa Y, Wang Z, Kerns J, et al. Inhibition of hepatoma cell growth *in vitro* by arylating and non-arylated K vitamin analogs. Significance of protein tyrosine phosphatase inhibition. *J Biol Chem* 1999;274:34803-34810.
65. Sun L, Yoshii Y, Miyagi K, Ishida A. Proliferation inhibition of glioma cells by vitamin K2. *No Shinkei Geka* 1999;27:119-125. [Article in Japanese]
66. Yaguchi M, Miyazawa K, Otawa M, et al. Vitamin K2 therapy for a patient with myelodysplastic syndrome. *Leukemia* 1999;13:144-145.
67. Nishikawa Y, Carr BI, Wang M, et al. Growth inhibition of hepatoma cells induced by vitamin K and its analogs. *J Biol Chem* 1995;270:28304-28310.
68. Miyazawa K, Yaguchi M, Funato K, et al. Apoptosis/differentiation-inducing effects of vitamin K2 on HL-60 cells: dichotomous nature of vitamin K2 in leukemia cells. *Leukemia* 2001;15:1111-1117.
69. Sakai I, Hashimoto S, Yoda M, et al. Novel role of vitamin K2: a potent inducer of differentiation of various human myeloid leukemia cell lines. *Biochem Biophys Res Commun* 1994;205:1305-1310.

70. Yaguchi M, Miyazawa K, Katagiri T, et al. Vitamin K2 and its derivatives induce apoptosis in leukemia cells and enhance the effect of all-trans retinoic acid. *Leukemia* 1997;11:779-787.
71. Yaguchi M, Miyazawa K, Otawa M, et al. Vitamin K2 selectively induces apoptosis of blastic cells in myelodysplastic syndrome: flow cytometric detection of apoptotic cells using APO2.7 monoclonal antibody. *Leukemia* 1998;12:1392-1397.
72. Takami A, Nakao S, Ontachi Y, et al. Successful therapy of myelodysplastic syndrome with menatetrenone, a vitamin K2 analog. *Int J Hematol* 1999;69:24-26.
73. Fujita H, Tomiyama J, Tanaka T. Vitamin K2 combined with all-trans retinoic acid induced complete remission of relapsing acute promyelocytic leukaemia. *Br J Haematol* 1998;103:584-585.
74. Miyazawa K, Nishimaki J, Ohyashiki K, et al. Vitamin K2 therapy for myelodysplastic syndromes (MDS) and post-MDS acute myeloid leukemia: information through a questionnaire survey of multi-center pilot studies in Japan. *Leukemia* 2000;14:1156-1157.
75. Jancin B. Vitamin K cuts hepatocellular CA mortality. *Fam Pract News* 2002;32:16.
76. Bendich A, Langseth L. Safety of vitamin A. *Am J Clin Nutr* 1989;49:358-371.
77. <http://www.nap.edu/openbook.php?isbn=0309072794> [Accessed July 31,2009]
78. Dowd P, Zheng ZB. On the mechanism of the anticlotting action of vitamin E quinone. *Proc Natl Acad Sci U S A* 1995;92:8171-8175.
79. Booth SL, Golly I, Sacke JM, et al. Effect of vitamin E supplementation on vitamin K status in adults with normal coagulation status. *Am J Clin Nutr* 2004;80:143-148.
80. Booth SL, Centurelli MA. Vitamin K: a practical guide to the dietary management of patients on warfarin. *Nutr Rev* 1999;57:288-296.
81. Hendler SS, Rorvik DR, eds. *PDR for Nutritional Supplements*. Montvale, NJ: Medical Economics Company, Inc; 2001.
82. Koitaya N, Ezaki J, Nishimuta M, et al. Effect of low dose vitamin K2 (MK-4) supplementation on bio-indices in postmenopausal Japanese women. *J Nutr Sci Vitaminol (Tokyo)* 2009;55:15-21.
83. Crowther MA, Donovan D, Harrison L, et al. Low-dose oral vitamin K reliably reverses over-anticoagulation due to warfarin. *Thromb Haemost* 1998;79:1116-1118.