Vitamin K

SCIENTIFIC NAME
Phytonadione (K1), Menaquinone (K2), Menadione (K3), Menadiol (K4), 4-amino-2-methyl-1-naphthol (K5)
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FAMILY

Other Common Names

Vitamin K1: Methylphytyl Naphthoquinone, Phylloquinone, Phytomenadione, Phytonadione, 2-Methyl-3-Phytyl-1,4-Naphthoquinone.

Vitamin K2: Menaquinone, Ménaquinone, Menatetrenone, Menatétrenone, MK-1, MK-2, MK-4, MK-5, MK-6, MK-7, MK-8, MK-9, MK-10, MK-11, MK-12, MK-13.

Vitamin K3: Menadione, Ménadione, Menadione Sodium Bisulfite, 2-Methyl-1,4-Naphthoquinone.

Vitamin K4: Menadiol, Menadiol Acetate, Menadiol Diacetate, Menadiol Sodium Diphosphate, Menadiol Sodium Phosphate, Menadiolum Solubile Methylnaphthohydroquinone.

Vitamin K5: 4-Amino-2-Methyl-1-Naphthol.

Fat-Soluble Vitamin, Vitamina K, Vitamine K, Vitamine Liposoluble, Vitamine Soluble dans les Graisses.

Overview

Vitamin K refers to a group of chemically similar, fat-soluble compounds called naphthoquinones (91449). The name vitamin K comes from the German word Koagulationsvitamin (57). Vitamin K1, also known as phytonadione or phylloquinone, is found in plants such as green leafy vegetables and vegetable oils (64). Vitamin K2, the menaquinones (MK), are made by bacteria in the human gut or consumed in foods such as cheese (64). Vitamin K1 and vitamin K2 (MK-4) are available in North America, while other forms (e.g. vitamin K3 and vitamin K4) are not (15,17).

Safety

LIKELY SAFE ...when vitamin K1 (phytonadione) or vitamin K2 (menaquinone) is used orally and appropriately. Vitamin K1 up to 10 mg daily and vitamin K2 up to 45 mg daily have been safely used in clinical trials lasting up to 2 years. A tolerable upper intake level for vitamin K in adults has not been set (54,55,58,6799,7135,14364). ...when vitamin K1 (phytonadione) is used parenterally and appropriately. Vitamin K1 (phytonadione) in oral and injectable form is an FDA-approved drug (7135).

POSSIBLY SAFE ...when vitamin K1 (phytonadione) 0.1% is used topically in a cream or ointment for up to 12 weeks (91455,103919).

CHILDREN: **LIKELY SAFE** ...when vitamin K1 (phytonadione) is used orally or parenterally and appropriately. Vitamin K1 (phytonadione) in oral and injectable form is FDA approved for use in children. A tolerable upper intake level for vitamin K in children has not been set (7135).

PREGNANCY AND LACTATION: **LIKELY SAFE** ...when used orally in amounts that do not exceed the daily adequate intake level (AI). A tolerable upper intake level for vitamin K in pregnancy and lactation has not been set (7135).

Adverse Effects

General: Orally, vitamin K is generally well tolerated.

Most Common Adverse Effects:

Orally: Diarrhea, nausea, and stomach upset.

Serious Adverse Effects (Rare):

Intravenously: There have been rare cases of anaphylaxis and hyperbilirubinemia (in infants).

Dermatologic

Orally, intake of vitamin K2 (menaquinone) along with calcium and vitamin D3 can cause an increased incidence of skin and skin appendage lesions compared to taking calcium and vitamin D3 alone. However, the risk of this adverse event is low, with 0.5 incidences per 100 patient-years occurring for patients treated with vitamin K, calcium, and vitamin D3 and 0.1 incidences per 100 patient-years occurring for patients treated with calcium and vitamin D3 alone (85467).

Gastrointestinal

Orally, vitamin K can cause mild to moderate gastrointestinal side effects (91450,91451). The most common effects include nausea, abdominal pain, and diarrhea (91450,91451).

Hepatic

Orally, vitamin K3 (menadione) has been linked to hepatotoxicity. Vitamin K3 is no longer used therapeutically in North America because it has been linked to hepatic toxicity and jaundice in animal research (7135).

Other

Intravenously, vitamin K can cause reactions that resemble hypersensitivity or anaphylaxis (85389). These reactions are rare. It is unclear whether the adverse effect is caused by the drug or a component of the solution. There have been very rare cases of hyperbilirubinemia, particularly in premature neonates, following large doses of vitamin K (15). One clinical study in premature infants shows that intramuscular administration of vitamin K 1.0 mg increases bilirubin levels and the duration of phototherapy when compared with vitamin K 0.3 mg and 0.5 mg. However, the clinical relevance of these findings is unclear, as no differences in bilirubin-induced neurologic dysfunction were reported (112100).

Effectiveness

EFFECTIVE

Hemorrhagic disease. Oral or intramuscular vitamin K1 is effective for preventing hemorrhagic disease in newborns.
Details: Vitamin K1 (phytonadione) administered orally or intramuscularly can prevent classic hemorrhagic disease of newborns (15,85367,85484). A single intramuscular administration of vitamin K1 1 mg is considered to be the most effective method, while oral administration of three doses of vitamin K1 1-2 mg over 8 weeks is considered to be an acceptable alternative (85506).

The effects of vitamin K on late hemorrhagic disease of newborns is less clear (85367,85484). In the Netherlands, an oral dose of 25 mcg daily for 3 months was used until 2011, when it was increased to 150 mcg daily. A reduction of late intracranial vitamin K deficiency bleeding in the general pediatric population, from 1.6 per 100,000 to 1.3 per 100,000, was associated with this dose increase (102351).

The effect of various doses of intramuscular birth vitamin K prophylaxis has also been investigated in premature infants. A small clinical study in premature infants born at or before 32 weeks gestation or who weigh 1500 grams or less shows that administering intramuscular vitamin K1 at doses of 0.3, 0.5, or 1.0 mg (Kenadione, Samarth Life Sciences PVT Ltd) within 1 hour of admission to the neonatal intensive care unit improves subclinical vitamin K deficiency. While infants in all 3 dosing groups had sufficient vitamin K levels at 5 days old, by day 28 those who were initially administered vitamin K 0.3 mg had higher rates of subclinical vitamin K deficiency and lower rates of vitamin K sufficiency. Rates of intraventricular or periventricular hemorrhage, pulmonary hemorrhage, necrotizing enterocolitis, and mortality did not differ across dosing groups (112100).

Hypoprothrombinemia. Oral or parenteral vitamin K1 is effective for treating and preventing hypoprothrombinemia.
Details: Vitamin K1 (phytonadione) 2.5-25 mg, used orally or parenterally, can prevent and treat hypoprothrombinemia caused by vitamin K deficiency or induced by salicylates, sulfonamides, quinine, quinidine, or broad-spectrum antibiotic therapy (15).

Vitamin K-dependent clotting factors deficiency (VKCFD). Oral and intravenous vitamin K1 is the primary treatment for VKCFD.
Details: Oral supplementation with vitamin K 10 mg two to three times weekly seems to prevent major hemorrhages and reduce mucocutaneous bleeding in individuals with VKCFD. Also, intravenous vitamin K may improve the prothrombin time-international normalized ratio (PT-INR) values in these patients. While vitamin K supplementation is the primary treatment method for VKCFD, the response to treatment varies significantly (85481).

Warfarin anticoagulation. Oral and intravenous vitamin K1 reverse warfarin-related excessive anticoagulation. Evidence for the use of oral vitamin K1 in patients with an unstable INR is conflicting.
Details: Taking vitamin K1 (phytonadione) orally or parenterally, but not subcutaneously, can counteract excessive warfarin anticoagulation and restore therapeutic international normalized ratio (INR) levels. Usually a single dose of 1-5 mg is used (85406,85425,85429).

Vitamin K might also be effective for stabilizing warfarin anticoagulation in patients with low intake of vitamin K. Patients with a low dietary vitamin K intake are significantly more likely to have an unstable INR than those who ingest higher amounts of vitamin K (16803). It is thought that vitamin K-depleted patients become more sensitive when vitamin K is ingested, even in small quantities, resulting in erratic or unstable INR (16804). One small clinical study and one small retrospective chart review show that taking oral vitamin K1 (phytonadione) 100-150 mcg daily improves INR stability in patients taking warfarin who previously had an unstable INR (16805,16806). However, a larger clinical study found no significant differences in INR stability in patients taking vitamin K 100 mcg daily when compared with placebo (16807). Also, some research suggests that, although taking vitamin K 1250 mcg daily may reduce INR in patients with excessive warfarin anticoagulation more significantly than placebo, there may not be a significant difference in the risk of bleeding complications (23380). It is important to keep in mind that, if a patient is stabilized on warfarin therapy plus vitamin K supplementation, discontinuing vitamin K can significantly increase the INR within 2-3 weeks after discontinuation (17714).

The most recent guidelines by the American College of Chest Physicians do not recommend routine use of vitamin K supplementation for patients on warfarin therapy with unstable INR (94926). However, the previous guidelines recommended vitamin K 100-200 mcg daily for these patients. Therefore, some providers still use vitamin K for this purpose (16808).

POSSIBLY EFFECTIVE

Osteoporosis. Oral vitamin K might reduce the risk of fractures and bone loss in patients with osteoporosis. However, it may not be beneficial in patients at risk for developing osteoporosis.
Details: Although observational and clinical research on dietary and supplemental vitamin K for osteoporosis has been conflicting (14364,85392,85445,102354,112106), overall, vitamin K supplementation seems to slightly reduce fracture risk (102354). A meta-analysis combining data from 36 heterogeneous studies in osteoporotic or postmenopausal patients shows that taking different regimens of either vitamin K1 or vitamin K2 is associated with a small reduction in clinical fractures (from 3.1% to 2.2%), but not with changes in vertebral fractures or BMD when compared with control (102354). This analysis is limited by the high variability in study designs and a lack of subgroup analyses stratifying different patient populations and forms of vitamin K.

In contrast, a meta-analysis of 16 studies in postmenopausal adults shows that taking various forms of vitamin K2 improves lumbar spine BMD based on 10 studies, especially when combined with other therapies such as vitamin D, calcium, or alendronate. However, vitamin K2 does not improve hip, femoral neck, or forearm BMD when compared with placebo. Furthermore, meta-analyses of 25 studies show that vitamin K2 does not reduce the incidence of fractures when compared with control (91451,112106). However, a sensitivity analysis that excluded the largest negative study of over 4000 postmenopausal Japanese females with mild osteoporosis (85456), shows that vitamin K2 45 mg daily reduces the risk of fractures by 53% and improves lumbar and vertebral BMD in patients with osteoporosis when compared with control (91451). This effect was not seen in patients without osteoporosis (91451). Vitamin K2 also does not seem to benefit patients with osteopenia. A recent clinical trial in postmenopausal patients with osteopenia shows that taking a larger dose of vitamin K2 (375 mcg, MK-7) with calcium 800 mg and vitamin D 1500 IU daily for 3 years does not seem to affect BMD, bone turnover, or bone microarchitecture when compared with placebo (105035).

Vitamin K1 (phytonadione) has also been evaluated, with mixed findings. One clinical study in postmenopausal patients with osteopenia shows that taking vitamin K1 5 mg daily with calcium 1500 and vitamin D 800 IU for up to 4 years reduces clinical fractures, but does not reduce clinical fragility fractures or improve BMD, when compared with placebo and vitamin D with calcium (85453). In healthy, non-osteoporotic patients ages 60-80 years, one clinical study shows that taking vitamin K1 500 mcg daily with calcium 600 mg and vitamin D 400 IU for 3 years does not affect BMD, despite increased plasma vitamin K levels and reduced undercarboxylated osteocalcin concentrations, when compared with taking calcium and vitamin D alone (16404). The same null effect on BMD and a reduced undercarboxylated osteocalcin was shown in a small clinical study in patients with Crohn disease without osteoporosis, taking vitamin K1 1-2 mg in combination with vitamin D3 400 IU and calcium 500 mg daily for 12 months (91454).

POSSIBLY INEFFECTIVE

Intraventricular hemorrhage. Oral vitamin K does not reduce the risk of periventricular hemorrhage in preterm infants.
^ Details: A meta-analysis of results from clinical research shows that administering vitamin K to pregnant patients at risk for very preterm birth does not reduce the overall risk of periventricular hemorrhage in preterm infants, perinatal mortality, or the associated neurological injury by the age of 7 years when compared to control. A subgroup analysis shows that vitamin K might reduce the risk of severe periventricular hemorrhage by 42% in preterm infants. However, when trials with inadequate blinding were excluded, this result was not statistically significant (85469).

INSUFFICIENT RELIABLE EVIDENCE to RATE

Athletic performance. It is unclear if oral vitamin K2 improves athletic performance.
^ Details: A small clinical study shows that taking vitamin K2 (menaquinone) 320 mcg orally daily for 4 weeks followed by 160 mg daily for 4 weeks, increases maximal cardiac output by 12% when compared with placebo in trained athletes performing standardized cycle ergometer exercise tests (95937).

Beta-thalassemia. Oral vitamin K2 has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: Preliminary clinical research shows that taking the menaquinone-7 (MK-7) form of vitamin K2 50 mcg daily plus vitamin D3 (calcitriol) 5 mcg daily for 12 months modestly improves bone mineral density (BMD) at the lumbar spine when compared to baseline in children with beta-thalassemia aged 3-18 years (91456). It is not clear if this improvement can be attributed to vitamin K, vitamin D3, or the combination.

Breast cancer. It is unclear if dietary intake of vitamin K2 reduces the risk of breast cancer.
^ Details: Population research has found that higher dietary intake of vitamin K2 (menaquinone) or vitamin K1 (phytonadione) is not associated with a reduced risk of premenopausal or postmenopausal breast cancer (85474).

Cancer. It is unclear if dietary intake of vitamin K reduces the risk of cancer or cancer-related mortality.
^ Details: One large population study involving healthy German patients has found that consuming more than 42-46 mcg of vitamin K2 (menaquinone) daily is associated with a 27% reduced risk of cancer mortality, but not cancer incidence, when compared with consuming less than 23-26 mcg daily. Dietary intake of vitamin K1 (phytonadione) was not associated with the risk of cancer or cancer mortality (85474). Another population study involving Mediterranean patients at high risk for cardiovascular disease has found that consuming about 630 mcg of vitamin K1 daily is associated with a 46% lower risk of cancer mortality when compared with consuming about 171 mcg of vitamin K1 daily. However, higher dietary intake of vitamin K2, 87 mcg daily, was not associated with a lower risk of cancer mortality when compared to those with lower dietary intake (79 mcg daily) (91452). Reasons for these discrepancies may relate to the definitions for high and low intake, the use of different databases to calculate vitamin K intake, and the different populations studied.

Cardiovascular disease (CVD). It is unclear if dietary or supplemental vitamin K reduces the risk of CVD events; the available research is conflicting.
^ Details: Most population research, including a meta-analysis of 21 observational cohort studies, has found that dietary intake of vitamin K1 (phytonadione) or vitamin K2 (menaquinone) is not associated with reduced risk for most cardiovascular events, such as CVD mortality, nonfatal MI, or stroke, although there might be a slightly reduced risk for CHD (85414,85482,91452,102353,103922).

However, some population studies have found benefit. Observational research in a Danish cohort aged 50-65 years with no history of atherosclerotic cardiovascular disease at baseline shows that those in the highest quintile of dietary vitamin K1 intake have a 21% lower risk of CVD-related hospitalization and complications, such as ischemic heart disease, ischemic stroke, or peripheral artery disease, over 17-22 years when compared with the lowest quintile of intake. This inverse association tapers off at intakes above 100 mcg daily. For vitamin K2 intake, the highest quintile has a 14% lower risk of hospitalization when compared with the lowest quintile, although the association is U-shaped, indicating an increased risk at high doses. The researchers theorize that this may be due to the fact that vitamin K2-rich foods include cheese, eggs, and butter (109910,109920).

There is also interest in using vitamin K to slow aortic valve calcification (AVC) and coronary artery calcification (CAC), which are CVD risk factors. In healthy patients ages 60-80 years with pre-existing CAC, taking a multivitamin with vitamin K1 (phytonadione) 500 mcg orally daily for 3 years reduces CAC progression by 6% when compared with the multivitamin alone (85461). However, research in patients with AVC has found no benefit. One small clinical study in patients on hemodialysis shows that taking the menaquinone-7 form of vitamin K2, 200 mcg orally daily for 1 year, does not affect the rate of AVC progression when compared with placebo (102352). Also, clinical research in males with significant AVC shows that taking the menaquinone-7 form of vitamin K2 720 mcg and vitamin D 25 mcg orally daily for 2 years does not reduce the rate of AVC progression or the rate of cardiovascular events, heart valve surgery, or all-cause mortality when compared with placebo (109916).

Cataracts. It is unclear if dietary vitamin K reduces the risk of cataracts in older adults.
^ Details: A secondary analysis of results from clinical research has found that higher dietary vitamin K1 (phytonadione) intake over a mean 5.6 years' follow-up is associated with a lower risk of cataracts and a lower incidence of cataract surgery in older adults at high risk for cardiovascular disease. The hazard ratio for developing cataracts was 0.71 and the hazard ratio for cataract surgery was 0.75 for people in the highest tertile of dietary vitamin K1 intake when compared with the lowest tertile (95936).

Cognitive impairment. It is unclear if dietary vitamin K alters the rate of decline in adults with cognitive impairment.
^ Details: Clinical research in adults aged 55-75 years with overweight or obesity, metabolic syndrome, and cognitive impairment shows that the largest increases in dietary vitamin K intake over a 2-year period are linked to a slower rate of cognitive decline when compared with the lowest increases in intake. This is demonstrated by higher scores on the mini-mental state examination (MMSE) and verbal fluency tests, and a greater number of patients maintaining an MMSE score of at least 24 (109919).

Colorectal cancer. It is unclear if dietary intake of vitamin K2 reduces the risk of colorectal cancer.
^ Details: Population research has found that higher dietary intake of vitamin K2 (menaquinone) or vitamin K1 (phytonadione) is not associated with a reduced risk of colorectal cancer (85474).

Cystic fibrosis. It is unclear if oral vitamin K improves coagulopathy in patients with cystic fibrosis.
^ Details: Suboptimal vitamin K status is common in patients with cystic fibrosis, especially those with pancreatic insufficiency, due to problems with fat digestion (85359,85479). Preliminary clinical research in patients with cystic fibrosis shows that taking vitamin K 1-5 mg orally for one month might decrease osteocalcin levels when compared with baseline, which suggests a lower risk of bone fractures (103920). Also, a small clinical trial in adults and children with cystic fibrosis and pancreatic insufficiency shows that taking a supplement containing fat-soluble vitamins A, D, E, and K for an average of 8.6 months reduces the number of patients with abnormal levels of protein induced by vitamin K absence (PIVKA-II), a defective form of prothrombin (85374).

Depression. It is unclear if dietary intake of vitamin K reduces depression.
^ Details: Population research has found that a dietary intake of vitamin K greater than 232 mcg daily is associated with reduced odds of depressive symptoms when compared with intakes of less than 83 mcg daily in older adults who are not taking vitamin D supplements. For every 100 mcg increase in vitamin K intake per day, the study found an 18% reduction in odds of depressive symptoms. However, there was no association identified in individuals taking vitamin D (100181). The effect of vitamin K for the prevention or treatment of clinical depression has not been investigated.

Diabetes. It is unclear if oral vitamin K1 improves glycemic control in patients with diabetes.
^ Details: A small clinical study in patients with diabetes who are taking oral antidiabetes medications shows that taking vitamin K2 (MK-7) 180 mcg twice daily for 12 weeks seems to reduce glycated hemoglobin by 1.6%, compared with a slight increase in the placebo group (105034). This study is limited due to high dropout rate in the placebo group.

EGFR inhibitor-induced acneiform rash. It is unclear if topical vitamin K is beneficial for the treatment or prevention of acneiform rash caused by EGFR inhibitors.
^ Details: Preliminary clinical research in adults receiving treatment with cetuximab, an EGFR inhibitor, shows that applying vitamin K1 (phytonadione) 0.1% cream (Vigorskin, Merck Serono SpA) twice daily to the face and trunk for 12 weeks may modestly reduce the percentage of patients who develop a moderate to severe acneiform rash (91455). The validity of this finding is limited by the lack of a control group. In patients with an existing rash after receiving the EGFR inhibitors cetuximab and panitumumab, a small clinical study shows that applying vitamin K1 (phytonadione) 1% ointment twice daily for 8 weeks to half of the affected area does not reduce the number of acneiform eruptions when compared with using placebo ointment on the other half of the affected area (103919). Patients in this study were allowed to use concomitant antibiotics and moisturizing agents, which may have confounded the results.

Kidney failure. It is unclear if oral vitamin K2 reduces the incidence or severity of muscle cramps in adults with kidney failure.
^ Details: Preliminary clinical research in patients on maintenance hemodialysis for at least 3 months with treatment-resistant muscle cramps shows that taking the menaquinone form of vitamin K2 360 mcg orally daily for 8 weeks reduces the frequency, severity, and duration of muscle cramps when compared with placebo (109917).

Kidney transplant. It is unclear if vitamin K is beneficial for reducing cardiovascular risk in kidney transplant recipients.
^ Details: Preliminary clinical research in adults with a stable kidney transplant for at least 1 year shows that taking vitamin K (menadiol diphosphate) 5 mg three times weekly for 1 year does not reduce aortic stiffness or coronary artery calcification, which are markers of cardiovascular disease, when compared with placebo (109913). The effects of long-term supplementation are unclear. Additionally, another very small study in adult kidney transplant recipients with vitamin K deficiency shows that taking supplemental vitamin K2 360 mcg daily for 12 weeks improves vitamin K status and prevents the progression of arterial stiffness but does not reduce serum calcification propensity when compared with placebo (112132).

Liver cancer. Small clinical studies suggests that vitamin K2 reduces mortality and the risk for hepatocellular carcinoma recurrence.
^ Details: Meta-analyses of 9-11 small clinical trials in patients with resectable hepatocellular carcinoma show that adding vitamin K2 45 mg daily for up to 3 years seems to reduce cancer recurrence by 9.5% and reduce the risk of mortality by 7% when compared with control. Meta-analyses of 3-4 small clinical trials in patients with non-resectable carcinoma show that taking vitamin K2 45 mg for up to 2 years seems to reduce cancer recurrence by 3% and reduce mortality by 16% when compared with control (105032). Most of the included studies were conducted in Japan, so it is unclear if these results are generalizable to other geographic locations.

Liver disease. It is unclear if dietary intake of vitamin K reduces the risk of liver disease.
^ Details: A small observational study in patients with chronic liver failure due to cholestatic liver disease has found that receiving intramuscular vitamin K1 10 mg daily for an average of 16 days is associated with a lower risk of death when compared with control (103926).

Lung cancer. It is unclear if dietary intake of vitamin K reduces the risk of lung cancer.
^ Details: Population research has found that consuming greater than 42-46 mcg of vitamin K2 (menaquinone) daily is associated with a 62% lower risk of lung cancer occurrence and a 59% lower risk of lung cancer mortality when compared to those who consume less than 23-26 mcg of vitamin K2 daily. Dietary intake of vitamin K1 (phytonadione) is not associated with a reduced risk of lung cancer or lung cancer mortality (85474).

Multiple sclerosis (MS). It is unclear if topical vitamin K reduces cutaneous adverse effects of MS treatment.

^ Details: In patients with relapsing-remitting MS, burning and pain can accompany subcutaneous interferon treatment. Preliminary clinical research shows that topical application of vitamin K cream (dose not specified) for 8 weeks reduces burning by approximately 8% and pain by 9% when compared with no prophylactic treatment. Redness of the skin is also reduced with vitamin K (91453).

Overall mortality. It is unclear if dietary intake of vitamin K reduces overall mortality.
^ Details: Observational research in healthy older adults has found that serum vitamin K levels 0.5 nmol/L or less, which corresponds to consuming about 50% of the recommended vitamin K adequate intake, is associated with a 19% higher risk of overall mortality when compared with higher serum levels of vitamin K (103922). In a Danish cohort of adults with a median age of 56 years at baseline, the comparative risk for all-cause mortality between the highest and lowest quintiles of K1 intake over a period of 17-23 years was 0.76. The risk for cardiovascular mortality was 0.72, and the risk of cancer-related mortality in smokers or former smokers, specifically, was 0.8. However, the correlation tapered off above a daily intake of 100 mcg (109911).

Pancreatic cancer. It is unclear if dietary intake of vitamin K reduces the risk of pancreatic cancer.
^ Details: Observational research in over 100,000 Americans aged 55-74 years at baseline has found no association between dietary vitamin K2 intake and pancreatic cancer incidence over an average follow-up of 9 years. However, the hazard ratio for development of pancreatic cancer was 0.57 for the highest quintile of dietary vitamin K1 intake when compared with the lowest quintile (109912).

Polycystic ovary syndrome (PCOS). It is unclear if vitamin K improves PCOS symptoms.
^ Details: Small clinical study in patients with PCOS show that taking vitamin K2 (menaquinone-7) 90 mcg daily for 8 weeks does not reduce fasting blood glucose, acne, hirsutism, or weight, although it improves depression and seems to reduce fasting insulin, when compared with placebo (105036,109918).

Prostate cancer. It is unclear if dietary intake of vitamin K reduces the risk of prostate cancer.
^ Details: Population research has found that higher dietary intake of vitamin K2 (menaquinone), but not vitamin K1 (phytonadione), is associated with a reduced risk of prostate cancer, particularly advanced prostate cancer (85443,85474).

Rheumatoid arthritis (RA). It is unclear if oral vitamin K improves RA symptoms.
^ Details: One small clinical study in patients with RA shows that adding the MK-7 form of vitamin K2 (menaquinone) 100 mcg daily to treatment with conventional antirheumatic agents for 3 months improves disease activity and inflammatory markers when compared with antirheumatic agents alone. When compared to the control group, vitamin K2 reduced disease activity scores by 41% (91449). However, another small clinical study in patients with mild to moderate RA shows that taking vitamin K1 (phytonadione) 10 mg daily for 8 weeks with conventional antirheumatic agents does not improve disease activity or inflammatory markers when compared with placebo (100182). These contrasting outcomes may be related to the type of vitamin K used, the duration of treatment, and the severity of the illness.

Rosacea. Although there is interest in using topical vitamin K1 for rosacea, there is insufficient reliable information about the clinical effects of vitamin K for this condition.

Stroke. It is unclear if dietary intake of vitamin K1 reduces the risk of stroke.
^ Details: Population research has found that higher dietary intake of vitamin K1 is not associated with a reduced risk of stroke (85482).

Wound healing. Although there is interest in using topical vitamin K1 for wound healing, there is insufficient reliable information about the clinical effects of vitamin K for this condition.

More evidence is needed to rate vitamin K for these uses.

Dosing & Administration

- **Adult**

  Oral:

  General: There is insufficient information to determine recommended dietary allowances (RDAs) for vitamin K, although some agencies have developed daily adequate intake (AI) recommendations. The Food and Nutrition Board (FNB) recommends 120 mcg for males over 19 years, 90 mcg for females over 19 years, and 90 mcg for pregnant or lactating adults over 19 years (7135). The European Food Safety Authority (EFSA) set the AI for vitamin K1 (phylloquinone) at 70 mcg for all adults, including those who are pregnant or breastfeeding (103924).

  Various doses of vitamin K1 and K2 have been used in clinical research. See Effectiveness section for condition-specific information.

  Consuming butter or other dietary fats in combination with vitamin K-containing foods, such as spinach, seems to increase vitamin K absorption when compared to eating vitamin K-containing foods alone (85510).

  Topical:

  Research is limited; typical dosing is unavailable.

- **Children**

  Oral:

  General: There is insufficient information to determine recommended dietary allowances (RDAs) for vitamin K, although some agencies have developed daily adequate intake (AI) recommendations. The Food and Nutrition Board (FNB) recommends 2 mcg at 0-6 months, 2.5 mcg at 7-12 months, 30 mcg at 1-3 years, 55 mcg at 4-8 years, 60 mcg at 9-13 years, and 75 mcg at 14-18 years (including those pregnant or lactating) (7135). The European Food Safety Authority (EFSA) recommends AIs for vitamin K1 (phylloquinone). These are 10 mcg at 7-11 months; 12 mcg at 1-3 years, 20 mcg at 4-6 years, 40 mcg at 7-10 years, 45 mcg at 11-14 years, and 65 mcg at 15-17 years (103924).

Various doses of vitamin K1 and K2 have been used in clinical research. See Effectiveness section for condition-specific information.

- **Standardization & Formulation**

  In clinical trials, oral vitamin K has been taken in soft-gel capsules (91449,91454). Vitamin K has also been taken as part of fortified multivitamins (85461) or in combination with fat-soluble vitamins (85374). Clinical trials have used various types of oral vitamin K, including vitamin K1 (phytonadione) (91454,100182) and the MK-7 form of vitamin K2 (menaquinone) (91449).

  Topical vitamin K1 has been applied in creams such as Vigorskin. This contains 0.1% vitamin K1, in a base of urea, wheat germ oil, hydrolyzed wheat protein, ceramides, and phytosphingosine (91455).

  Vitamin K is also used intravenously and intramuscularly (85367,85425).

Interactions with Drugs

WARFARIN (Coumadin)
Interaction Rating = **Major** Do not take this combination.
Severity = High • Occurrence = Likely • Level of Evidence = **C**
Vitamin K can antagonize and reverse the therapeutic effects of warfarin.
Details
Vitamin K antagonizes the effects of warfarin (15,23380,25507,25508,85425,85429). Excessive vitamin K intake, either from supplements or from changes in the diet, can reduce the anticoagulant effect of warfarin (15).

Interactions with Supplements

COENZYME Q10: Coenzyme Q10 has vitamin K-like activity and may have additive effects.
Details
Coenzyme Q10 is chemically similar to vitamin K2 (menaquinone) and can have vitamin K-like effects, including antagonism of warfarin (2128,6048). Concomitant use of coenzyme Q10 and vitamin K might increase the risk of clotting in people taking anticoagulants.

TIRATRICOL: Theoretically, tiratricol might antagonize the prothrombinemic effects of vitamin K.
Details
Tiratricol is related to thyroid hormones such as levothyroxine. Levothyroxine antagonizes the prothrombinemic effects of vitamin K by increasing catabolism of vitamin K-dependent clotting factors (15). It is not known if tiratricol has these effects.

VITAMIN A: Theoretically, large doses of vitamin A might antagonize the effects of vitamin K.
Details
Animal research has shown that high doses of vitamin A (retinoids) antagonize the effects of vitamin K. However, this interaction has not been reported in humans (7135,10560,25510).

VITAMIN E: Large doses of vitamin E might block the effects of vitamin K.
Details
Taking vitamin E in doses of at least 800 IU daily can antagonize the effects of vitamin K, increasing the risk of bleeding in people who are taking warfarin or have low vitamin K intakes (93,7135,25511). Vitamin E appears to reduce the absorption of vitamin K and to bind to vitamin K-dependent enzymes, preventing their activity (7135,11512).

Interactions with Conditions

BILIARY DISORDERS

Patients with biliary disorders might have impaired ability to absorb vitamin K. People with decreased bile secretion may require co-administration of supplemental bile salts to ensure adequate vitamin K absorption (15).

HEMODIALYSIS

There is concern that excessive vitamin K intake might increase soft tissue calcification in patients receiving hemodialysis. An observational study found that patients on hemodialysis with radiovisible ectopic calcifications had higher vitamin K1 blood levels when compared with patients on hemodialysis without calcifications (11744).

LIVER DISEASE

There is concern that high doses of vitamin K might worsen coagulation disorders in patients with severe liver disease. In severe liver disease, there is usually a lack of vitamin K activated coagulation factors produced by hepatocytes. Therefore, hypoprothrombinemia secondary to liver disease may be unresponsive to treatment with vitamin K (15).

Interactions with Lab Tests

17-HYDROXYCORTICOSTEROIDS

Theoretically, vitamin K might cause a false increase in urine tests for corticosteroids. In vitro research shows that vitamin K interferes with the Reddy method (275).

Nutrient Depletion

SOME DRUGS CAN AFFECT VITAMIN K LEVELS:

ANTIBIOTIC DRUGS

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Prolonged therapy with antibiotic drugs might decrease levels of vitamin K.

Details

Vitamin K produced by intestinal bacteria is absorbed from the ileum (4437,4439,9502). This contribution to overall vitamin K status is unclear, and likely varies (4439,7135). Destruction of vitamin K-producing bacteria by antibiotics can sometimes lead to vitamin K deficiency, prolonging clotting times and increasing bleeding risk (4439,9502,11513,11514,11515,11516). It's suggested that antibiotics such as cefamandole that are secreted into the bile in large amounts have a greater effect on vitamin K-producing bacteria (11514). Also, some cephalosporins have a methylthiotetrazole side chain that may interfere with vitamin K activity, directly inhibiting clotting factor production in the liver (4439,11516). These cephalosporins include cefamandole, cefoperazone, cefmetazole, and cefotetan. This interaction is most likely to occur with prolonged antibiotic therapy (10 days or more) in people with poor dietary vitamin K intake (11514,11515,11516). Vitamin K supplements aren't necessary for otherwise healthy people taking short courses of antibiotics. For information on foods that are rich in vitamin K, see our **chart**.

ANTICONVULSANTS

Depletion Rating = **Insignificant Depletion** A supplement is not needed for most patients.

Certain anticonvulsants might decrease levels of vitamin K in adults; some anticonvulsants may also decrease vitamin K levels in the fetus when taken during pregnancy.

Details

When taken during pregnancy, anticonvulsants that induce hepatic enzymes (e.g., phenobarbital, phenytoin, carbamazepine) can reduce vitamin K levels in the fetus and increase the risk of intracranial hemorrhage soon after birth (11521,11522,11523,11524,11525). It's thought that liver enzyme induction by these drugs increases vitamin K metabolism (11521,11522,11523,11525). This has a significant effect on vitamin K levels in infants, who haven't built up stores of the vitamin (11525). When anticonvulsants are needed during pregnancy, vitamin K 10-20 mg daily should be taken orally for the last month of pregnancy, and the baby should receive vitamin K immediately after delivery (11522,11525). There is also limited evidence that chronic carbamazepine or phenytoin therapy can cause subclinical reductions in vitamin K activity in adults. There are rare reports of prolonged clotting times and bleeding in people with additional risk factors for vitamin K deficiency, such as poor nutritional intake (10582,11533,11534). These anticonvulsants don't significantly affect vitamin K and clotting parameters in most children and adults. For information on foods that are rich in vitamin K, see our **chart**.

BILE ACID SEQUESTRANTS

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Bile acid sequestrants might decrease the absorption and levels of vitamin K.

Details

By reducing absorption of dietary fats, bile acid sequestrants may also reduce absorption of fat-soluble vitamins such as vitamin K. Some studies have found no changes in vitamin K levels or prothrombin times after up to 2 years of bile acid sequestrant use (4455,4460,10566). However, there are a few case reports of hypoprothrombinemia and bleeding, usually in people with other risk factors (4458,11519).

MINERAL OIL

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Mineral oil might decrease the absorption and levels of vitamin K.

Details

Mineral oil can reduce absorption of fat-soluble vitamins including vitamin K. Chronic use, both daily and intermittently, has been associated with prolonged clotting times (4495). Advise patients against regular or long-term use of mineral oil.

ORLISTAT (Xenical, Alli)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Orlistat might decrease the absorption and levels of vitamin K.

Details

Orlistat can reduce the absorption of some fat-soluble vitamins, although the extent of its effect on food-derived vitamin K hasn't been determined (1730). In healthy people, small decreases in plasma vitamin K levels can occur, usually without any change in clotting times (9595,10570). However, prolonged clotting times might occur when orlistat is added to warfarin therapy. This may be due to both direct effects of orlistat on vitamin K absorption, and reduced intake of vitamin K-rich fatty foods that cause unpleasant side effects with orlistat (11520). The manufacturer of orlistat recommends that all patients take a multivitamin supplement containing all fat-soluble vitamins, separating the dosing time by at least 2 hours from orlistat (1730).

RIFAMPIN (Rifadin)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Rifampin might decrease levels of vitamin K.

Details

There are occasional reports of vitamin K deficiency associated with rifampin therapy, leading to prolonged clotting times and, in one case, a cerebral bleed (11517,11518). Suggested mechanisms include reduced intestinal absorption of vitamin K, destruction of vitamin K-producing intestinal bacteria, and interference with enzymes that regenerate vitamin K from its inactive metabolite. Symptomatic vitamin K deficiency is most likely to occur in people with poor dietary intake or other contributory factors (11517,11518). For information on foods that are rich in vitamin K, see our **chart**.

Overdose

There is insufficient reliable information available about the presentation or treatment of overdose with vitamin K. A tolerable upper limit for vitamin K has not been established due to lack of known toxicity (7135).

Commercial Products Containing: Vitamin K

View All

View Health Canada Licensed Products

View Certified Products

USP Verified Products

NSF Contents Certified Products

NSF Certified for Sport Products

Pharmacokinetics

Absorption: The varying side chains of vitamin K differentiate the compounds in terms of intestinal absorption and bioavailability (57). The MK-1 and MK-7 forms of vitamin K2 (menaquinone) are well absorbed, with peak blood levels occurring 4 hours after intake (102352). Menaquinones MK-7 through MK-10 are synthesized by bacteria in the colon, but absorption from this location is limited (16403). Bile salts are required for oral absorption of vitamin K1 (phytonadione) and vitamin K2 (menaquinone), but not vitamin K4 (menadiol) (15). In human research, the oral absorption of vitamin K1 (phytonadione) from vegetables is 5% to 10%, and from supplements is approximately 13% (85435,109911); bioavailability from kale with added vegetable oil is about 5% (85476).

The absorption and bioavailability of oral vitamin K1 (phytonadione) from food depends on the type of food and/or meal that it is contained in. The presence of added fat or consumption of vitamin K1 in fat may increase absorption. Furthermore, diet types may also impact the amount of vitamin K1 that is absorbed and bioavailable (85435,85510).

Some research suggests that vitamin K1 is absorbed faster and better from a pharmaceutical concentrate (Konakion) when compared with a natural food source, such as spinach (85510). However, other studies have shown no difference in plasma increases of vitamin K1 when comparing supplementation of vitamin K1 from broccoli versus a vitamin K1-fortified oil (85358).

Distribution: The varying side chains of vitamin K differentiate the compounds in terms of transport and tissue distribution (57). Only small amounts of vitamin K are stored in body tissues (64). However, with adiposity, it appears that more vitamin K1 is stored in adipose tissue resulting in reduced levels in the blood circulation (85472).

At least the longer sidechain forms of vitamin K2 (menaquinone) are transported with both low-density lipoprotein (LDL)- and triacylglycerol-rich fractions of plasma lipoproteins, reaching the liver and many extrahepatic tissues. In contrast, vitamin K1 and shorter forms of vitamin K2 may be transported only with the triacylglycerol fraction and are mainly cleared by the liver (16405,91450).

Postmortem analysis has found that vitamin K1 may be recovered in all tissues, with the highest levels in the liver, heart, and pancreas, and lower levels in the brain, kidneys, and lungs (85509). The MK-4 form of vitamin K2 (menaquinone) has been recovered from the brain, kidneys, pancreas, heart, and lungs. In the brain and kidneys, levels of MK-4 are higher than vitamin K1. Other menaquinones (MK-6-11) have been recovered in the liver, heart, and pancreas (85509).

Metabolism: Some mammalian tissues, such as the pancreas, testes, and arterial vessel walls, are able to convert vitamin K1 into the MK-4 form of vitamin K2. Even at high dietary vitamin K1 intakes, the accumulated vitamin K in these tissues is almost exclusively MK-4 (16403). Vitamin K4 (menadiol) is a synthetic, water-soluble salt of vitamin K3 (menadione) and is converted to vitamin K3 in the liver (15). However, in humans, a single dose of three different types of vitamin K, namely vitamin K1 (phytonadione), and the menaquinone-4 and menaquinone-7 forms of vitamin K2, resulted in an approximately 5% to 25% increased catabolism to menadione (85423).

Polymorphisms in genes encoding enzymes involved in vitamin K metabolism, including vitamin K epoxide reductase and gamma-glutamyl carboxylase, play a role in plasma levels of vitamin K1 (phytonadione) (85463).

Excretion: In humans, a single dose of three different types of vitamin K, namely vitamin K1 (phytonadione), and the menaquinone-4, and menaquinone-7 forms of vitamin K2, results in increased vitamin K3 (menadione) excretion in the urine, peaking 3 hours after intake (85423). Vitamin K appears to be excreted in both urine and feces and the form and route of excretion may depend on the amount in the diet (85384). The MK-7 form of vitamin K2 (menaquinone) has a much longer half-life than the MK-1 form, resulting in more stable serum levels and accumulation during prolonged intake (102352).

Mechanism of Action

General: Vitamin K is a generic term for a group of related compounds with a common central ring structure, resulting in similar activity (57). Vitamin K1 (phytonadione, phylloquinone) is obtained from dietary sources, such as leafy green vegetables, broccoli, Brussels sprouts, plant oils, and margarine (57,7135,11285,109911). Vitamin K2 is a group of menaquinones which are classified by the length of their aliphatic, isoprenoid side chain, designated as MK-1 through MK-10, obtained from meat, cheese, and eggs, and synthesized by bacteria (64,16403,102352,109911). Vitamin K4 (menadiol) is a synthetic, water-soluble salt of vitamin K3 (menadione) and is converted to vitamin K3 in the body (15).

Symptomatic vitamin K deficiency is rare, usually occurring only with severe malnutrition or conditions causing gastrointestinal malabsorption such as extensive bowel resection (505,15556). It has also been reported in severely disabled, bedridden children on prolonged enteral tube feeding (15555), and after prolonged therapy with some antibiotics (4439,9502,11513,11514,11515,11516).

Anti-cataract effects: Preliminary clinical research suggests that a high dietary intake of vitamin K1 reduces the risk of cataracts in older adults, possibly due to anti-inflammatory and antioxidant effects (95936).

Anti-rheumatoid arthritis effects: In clinical research, the MK-7 form of vitamin K2 (menaquinone) improved the anti-inflammatory and analgesic effects of conventional antirheumatic agents when taken together. As shown in laboratory research, this may be due to beneficial effects of vitamin K on the proliferation and viability of synovial cells in the cartilage (91449).

Antidiabetes effects: In patients with well-controlled type 2 diabetes, taking vitamin K2 (menaquinone-7) 360 mcg daily for 12 weeks reduces atherogenic coefficient, triglyceride-glucose index, and atherogenic index of plasma when compared with placebo, but not after adjustment for baseline values. It also did not change lipoprotein indices or metabolic score for insulin resistance index (109914).

Blood clotting effects: Vitamin K is a coenzyme for the hepatic synthesis of blood coagulation factors II (prothrombin), VII (proconvertin), IX (Christmas factor or plasma thromboplastin component), and X (Stuart-Prower factor), and proteins C and S in the liver (57,7131,7135). Vitamin K is also involved in carboxylation of gamma-carboxyglutamate (Gla) proteins that facilitate binding of coagulation factors to platelets (57). In adequate doses, vitamin K reverses the inhibitory effects of coumarin and warfarin derivatives on the synthesis of clotting factors (15).

In healthy adults aged 25-40 years who are not receiving anticoagulants, taking vitamin K2 (menaquinone-7) 90 mcg orally daily for 30 days does not alter prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), or levels of clotting factors II, VII, IX, and X, when compared with baseline. This suggest that it does not alter hemostatic balance (109909).

Bone metabolism effects: Vitamin K is a cofactor for carboxylation of matrix Gla proteins, including osteocalcin, which is produced in osteoblasts, regulates accumulation of bone minerals including calcium, and promotes transition of osteoblasts to osteoclasts (6797,7130,7131,7135,15552,15553,102354,109915).

Undercarboxylated osteocalcin (ucOC, also called free osteocalcin) has a lower affinity for hydroxyapatite and therefore lower calcium binding (15553,15554). Increased serum levels of undercarboxylated osteocalcin are sometimes used as a marker of low vitamin K levels in bone, and supplementation with vitamin K and calcium decreases ucOC, increases carboxylated osteocalcin (cOC), and decreases the ratio of ucOC to cOC (56,6797,6798,7130,7131,7135,15553,106404,102354,109915,112106). However, the usefulness of osteocalcin levels is controversial due to variations in testing methodology and inconsistent clinical findings (7135). Higher ucOC levels have been linked to reduced bone mineral density (BMD) and an increased risk of hip fracture in elderly females (55,56,7130). Whether any form of supplemental vitamin K can improve BMD and reduce fracture rates is unclear as study results are conflicting (7130,16404). A meta-analysis of 10 trials shows that a combination of vitamin K1 or K2 and calcium is associated with increased lumbar spine BMD when compared with controls, but has no effect on total femoral or femoral neck BMD (109915). Some limited research also suggests that combining vitamin K with vitamin D improves BMD (103921).

There are other potential mechanisms of action for vitamin K that do not involve its ability to gamma-carboxylate proteins. Vitamin K may decrease bone resorption by decreasing prostaglandin E2 synthesis in osteoclasts, and by effects on calcium balance, and interleukin 6 production in bone (7131,15553). As shown in laboratory research, vitamin K might also increase bone formation by regulating the transcription of osteoblast markers involved in bone formation, including bone alkaline phosphatase, osteoprotegerin, osteopontin, and matrix Gla protein (85397).

Whether people taking vitamin K antagonists or oral anticoagulants are at increased risk of fracture is controversial (51,52,63,7134). Oral anticoagulants might have some effect on the BMD of the radius of the arm, but no effect on the bones of the hip and back (7135). The most pronounced effects of vitamin K antagonists appear to be on rapidly growing bone (7133).

Low serum and bone levels of vitamin K, and high ucOC levels are seen in patients with Crohn disease and are correlated with increased bone resorption and decreased BMD of the lumbar spine (15552,15553,15554). Factors contributing to low vitamin K levels in Crohn disease may include undernutrition, malabsorption, and bowel resections (15552,15553,15554).

Cardiovascular effects: Vitamin K might play a role in the prevention of atherosclerosis. The development of atherosclerosis is linked to low serum levels of vitamin K (53,57). Vitamin K is a cofactor for activation of matrix Gla-protein by carboxylation. This protein is found in blood vessel walls, where it inhibits vascular calcification (16405). Vascular vitamin K deficiency is thought to increase the amount of under-carboxylated, non-functional matrix Gla-protein, leading to increased calcification and atherosclerosis (95937). Some population research has found that higher dietary intake of vitamin K2, especially the MK-4 fraction, is associated with a reduced risk of coronary calcification (16405) and risk of and mortality from coronary heart disease (85482). Also, although there is some discrepancy, overall it appears that dietary intake of vitamin K1 does not affect cardiovascular outcomes (16405,85414,85482).

In hemodialysis patients, accelerated vascular calcification is common due to low intakes and circulating levels of vitamin K. The MK-7 form of vitamin K2 (menaquinone) appears to reduce levels of the undercarboxylated, non-functional matrix Gla-protein in these patients (91450). However, the MK-7 form of vitamin K2 does not seem to reduce the rate of vascular calcification seen in hemodialysis patients (102352).

Vitamin K2 is also thought to restore mitochondrial function in cardiac muscle, increasing production of adenosine triphosphate (ATP) and improving muscle function (95937). This might improve cardiac output during exercise and in people with heart failure.

Classifications

Fat-soluble Vitamins

References

See Monograph References

Monographs are reviewed on a regular schedule. See our Editorial Principles and Process for details. The literature evaluated in this monograph is current through 11/18/2024. This monograph was last modified on 9/9/2024. If you have comments or suggestions, please tell the editors.