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Vitamin K

DESCRIPTION

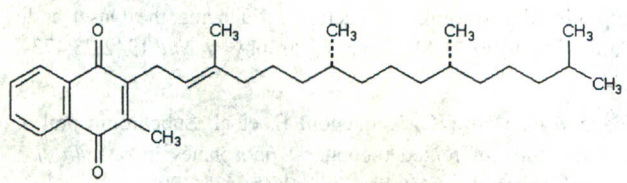
Vitamin K is a generic term for a group of substances which contain the 2-methyl-1, 4-naphthoquinone ring structure and which possess hemostatic activity. Substances with vitamin K activity were originally identified in green leafy vegetables, hemp seeds, liver and fish meal. These substances were found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

Vitamin K_1 or phylloquinone is the principal dietary source of vitamin K and its predominant circulating form. Green leafy vegetables are rich in vitamin K_1 and contribute 40%-50% of total dietary intake of the vitamin. The next largest contributors to dietary vitamin K intake are the vegetable oils olive oil, canola oil, soybean oil and cottonseed oil. These vegetable oils also contain vitamin K_1. Vitamin K_1 is a fat-soluble substance. Vitamin K_2, which is also fat soluble, is the collective term for a number of substances known as menaquinones. Vitamin K_2 is found in chicken egg yolk, butter, cow liver, certain cheeses and fermented soybean products such as natto. This form of vitamin K is also produced by certain bacteria, including some of the bacteria that comprise the microflora of the intestine. The dietary contribution of vitamin K_2 is much less than that of vitamin K_1. The amount of vitamin K contributed to the body by the intestinal microflora remains unclear. Vitamin K_3 or menadione is a fat-soluble synthetic compound which is used in animal feed and dog and cat food. It is metabolized to vitamin K_2.

Vitamin K is involved as a cofactor in the posttranslational gamma-carboxylation of glutamic acid residues of certain proteins in the body. These proteins include the vitamin K-dependent coagulation factors II (prothrombin), VII (proconvertin), IX (Christmas factor), X (Stuart factor), protein C, protein S, protein Zv and a growth-arrest-specific factor (Gas6). In contrast to the other vitamin K-dependent proteins in the blood coagulation cascade, protein C and protein X serve anticoagulant roles. The two vitamin K-dependent proteins found in bone are osteocalcin, also known as bone G1a (gamma-carboxyglutamate) protein or BGP, and the matrix G1a protein or MGP. Gamma-carboxylation is catalyzed by the vitamin K-dependent gamma-carboxylases. The reduced form of vitamin K, vitamin K hydroquinone, is the actual cofactor for the gamma-carboxylases. Proteins containing gamma-carboxyglutamate are called G1a proteins.

Vitamin K deficiency can occur under certain conditions. These include, inadequate dietary intake, malabsorption syndromes (cystic fibrosis, Crohn's disease, ulcerative colitis, Whipple's disease, celiac sprue, short bowel syndrome) and loss of storage sites due to hepatocellular disease. Vitamin K deficiency frequently occurs in those with chronic liver disease, such as primary biliary cirrhosis. Coumarin anticoagulants, such as warfarin, induce a state analogous to vitamin K deficiency by inhibiting the reduction and recycling of vitamin K, and certain cephalosporin antibiotics (see Interactions) may also induce a vitamin K deficiency state by inhibiting the reduction and recycling of the vitamin. Recently, it has been found that space flight may impair vitamin K metabolism and also induce a state of vitamin K deficiency. Symptoms of vitamin K deficiency include easy bruisability, epistaxis, gastrointestinal bleeding, menorrhagia and hematuria. Chronic vitamin K deficiency may also result in osteoporosis and increased risk of fractures. There is some evidence that chronic warfarin use may also cause osteoporosis.

Vitamin K_1, in addition to being known as phylloquinone, is also known as phytonadione and 2-methyl-3-phytyl-1, 4-naphthoquinone. The lipophilic side chain is located at position 3 of the naphthoquinone ring. Its molecular formula is $C_{31}H_{46}O_2$ and its molecular weight is 450.71 daltons. The structural formula is:



Vitamin K_1

Vitamin K_2 is the collective term for a group of vitamin K compounds called menaquinones. The menaquinone homolgues are characterized by the number of isoprene residues comprising the side chain. The side chain is located at position 3 of the naphthoquinone ring. The group chemical name of the menaquinones is 2-methyl-3-all-*trans*-polyprenyl-1, 4-naphthoquinones. Menaquinones with side chains of up to 15 isoprene units have been described. Menaquinones

of from two to 13 isoprene units have been found in human and animal tissues. Menaquinones are designated by the name menaquinone followed by a number. The number refers to the number of isoprene residues in the structure. Thus, menaquinone-4, abbreviated MK-4, possesses four isoprene residues in the side chain. Menaquinone-7 possesses seven isoprene units in the side chain. The menaquinones may also be designated by the number of carbons in the side chain. An isoprene residue contains five carbons. Thus, menaquinone-4 is also called vitamin K_2 (20) and menaquinone-7 is also called vitamin K_2 (35). Menaquinone-4 is also known as menatetrenone. The fermented soybean product natto is rich in menaquinone-7. Menaquinone-4 is the predominant form of vitamin K in the rat brain.

Vitamin K_3 or menadione is a synthetic naphthoquinone derivative. It is also known as 2-methyl-1, 4-naphthoquinone. Its molecular formula is $C_{11}H_8O_2$ and its molecular weight is 172.18 daltons. Vitamin K_3 does not possess a lipophilic side chain.

The nutritional supplement forms of vitamin K are vitamin K_1 and vitamin K_2.

ACTIONS AND PHARMACOLOGY

ACTIONS

Vitamin K has hemostatic activity and may have anti-osteoporotic, antioxidant and anticarcinogenic activities.

MECHANISM OF ACTION

The hemostatic activity of vitamin K is well known. Vitamin K is used to treat anticoagulant-induced prothrombin deficiency caused by warfarin, hypoprothrombinemia secondary to antibiotic therapy and hypoprothrombinemia secondary to vitamin C deficiency from various causes, including malabsorption syndromes. The pharmacological action of vitamin K in the treatment of hypoprothrombinemia is related to the normal physiological function of the vitamin. Vitamin K is an essential cofactor for the gamma-carboxylase enzymes which catalyze the posttranslational gamma-carboxylation of glutamic acid residues in inactive hepatic precursors of coagulation factors II, VII, IX and X. Gamma-carboxylation converts these inactive precursors into active coagulation factors which are secreted by hepatocytes into the blood. Supplement vitamin K has no hemostatic activity in those who are not vitamin K-deficient.

The mechanism of the possible anti-osteoporotic activity of vitamin K is not completely understood. Two vitamin K-dependent proteins are found in bone: osteocalcin or bone G1a protein (BGP) and the matrix G1a protein or MGP. Osteocalcin appears to be the most abundant non-collagenous protein in the bone. Most of the osteocalcin synthesized by the osteoblasts during bone matrix formation is incorporated into bone. This is due to the high specificity of the gamma-carboxyglutamyl residues for the calcium ions of hydroxyapatite. A small amount of osteocalcin is released into the circulation. Osteocalcin appears to act as a regulator of bone mineralization. High levels of circulating undercarboxylated (under-gamma-carboxylated) osteocalcin have been associated with low bone mineral density and increased risk of hip fractures. The serum level of undercarboxylated osteocalcin may be a more sensitive marker of vitamin K status than blood coagulation tests. High levels of undercarboxylated osteocalcin are frequently found in the context of normal blood coagulation tests.

In vivo and *in vitro* studies have shown that vitamin K may directly act on bone metabolism. *In vitro* studies have demonstrated that vitamin K_2 inhibits bone resorption by, in part, inhibiting the production of bone resorbing substances such as prostaglandin E_2 and interleukin-6. Vitamin K_2 has been reported to enhance human osteoblast-induced mineralization *in vitro* and to inhibit bone loss in steroid-treated rats and ovariecomized rats.

The reduced form of vitamin K, vitamin K-hydroquinone, is the active cofactor for the gamma-carboxylase enzymes. Vitamin K hydroquinone is produced in the vitamin K cycle. In the vitamin K cycle, vitamin K-hydroquinone is continuously regenerated. Vitamin K-hydroquinone is a potent reactive oxygen species scavenger. Vitamin K-hydroquinone has been found to inhibit lipid peroxidation.

Certain naphthoquinones, in particular the synthetic vitamin K menadione, have been found to have antitumor activity *in vitro* and *in vivo*. Vitamin K_2 has been found to induce the in vitro differentiation of myeloid leukemic cell lines. The mechanism of the possible anticarcinogenic activity of vitamin K is not well understood. Menadione is an oxidative stress inducer and its possible anticarcinogenic activity may, in part, be explained by induction of apoptotic cell death. One study suggested that the induction of apoptosis by menadione is mediated by the Fas/Fas ligand system. Another study reported that menadione induces cell cycle arrest and cell death by inhibiting Cda 25 phosphatase.

PHARMACOKINETICS

Vitamin K, mainly in the form of vitamin K_1, is principally absorbed from the jejunum and ileum. The efficiency of absorption is variable and ranges from 10% to 80%. Vitamin K is delivered to the enterocytes in micelles formed from bile salts and other substances. Vitamin K is secreted by enterocytes into the lymphatics in the form of chylomicrons. It enters the circulation via the thoracic duct and is carried in the circulation to various tissues including hepatic, bone and spleen, in the form of chylomicron remnants. In the liver, some vitamin K is stored, some is oxidized to inactive end products and some secreted with VLDL (very low-density

lipoprotein). Approximately 50% of vitamin K is carried in the plasma in the form of VLDL, about 25% in LDL (low-density lipoprotein) and about 25% in HDL (high-density lipoprotein). Vitamin K undergoes some oxidative metabolism. Excretion of vitamin K and its metabolites is mainly via the feces. Some urinary excretion of vitamin K also occurs.

INDICATIONS AND USAGE

Vitamin K is indicated in those with vitamin K deficiency, in some cases of hemorrhagic disease of the newborn, in some malabsorption syndromes and in some on long-term total parenteral nutrition. There is emerging evidence that adequate vitamin K intake may help protect against osteoporosis generally. There is the suggestion in early research that vitamin K may also have some anti-atherosclerotic effects. Claims that vitamin K is an anti-cancer agent derive from very preliminary work utilizing, primarily, vitamin K_3 or menadione. There is little or no reliable data yet available to support further claims that vitamin K inhibits platelet aggregation, that it has favorable effects on insulin and glucose, that it is helpful in Alzheimer's disease and that it favorably modulates immunity and has anti-inflammatory effects.

RESEARCH SUMMARY

Though primary vitamin K deficiency is uncommon, deficiencies secondary to disease or drug therapy arise more often. The most significant instance of acquired vitamin K deficiency manifests as hemorrhagic disease of the newborn (HDN). Causes of HDN are varied and include exclusive breast feeding (vitamin K is in short supply in breast milk) and liver dysfunction. Vitamin K prophylaxis, via oral and intramuscular administration at birth, has been widely used for decades with apparent efficacy. Intramuscular administration is considerably more effective but has been less used in recent years following publication of an epidemiological study suggesting an association between this treatment and a reported doubling of cancer risk in later life. Whether this association is genuinely causal has yet to be confirmed. No such association is seen with oral administration.

A number of drug therapies, including vitamin A and E in pharmacologic doses, some broad-spectrum antibiotics, the 4-hydroxycoumarins and salicylates, antagonize the action of vitamin K and, in some instances, result in deficiencies requiring additional vitamin K intake under a physician's supervision. TPN is frequently another indication for supplemental vitamin K, as are some malabsorption syndromes and gastrointestinal disorders. Those with parenchymal liver disease often have vitamin K deficiency. Recently vitamin K deficiency was found to be significant in many with cystic fibrosis.

Over the past decade, some very important vitamin K roles in bone metabolism have begun to be elucidated. Vitamin K has been demonstrated to promote the gamma-carboxylation of glutamyl residues on many bone proteins. This carboxylation is associated with increased bone mineral density, while undercarboxylation results in diminished bone mineral density and increased risk of bone fracture.

In a prospective analysis, the diets of 72,327 women 38-63 years of age were assessed and the incidence of hip fractures monitored over a ten-year period. A significant association was found between low dietary vitamin K intake and increased risk of hip fracture. This study looked at several specific dietary components and found a significant protective effect from lettuce, a source rich in vitamin K. Women who consumed lettuce (iceberg and romaine) one or more times daily had a significant 45% lower risk of hip fracture than did women who ate lettuce once a week or less.

In another study, gammacarboxyglutamate (Gla) proteins, the formation of which, as noted above, are promoted by vitamin K activity, were observed to play regulatory roles in calcification processes in both bone tissue and atherosclerotic vessel wall. This research suggested that reduced vitamin K status increases vessel wall calcification and reduces bone calcification and that increased vitamin K status might do the opposite.

A recent review of vitamin K research foresees the use of vitamin K in dietary supplements and in functional foods "for healthy individuals to prevent bone and vascular disease, as well as for patients on oral anticoagulant treatment to offer them protection against coumarin-induced side effects," which may include, among other things, accelerated bone loss. Long-term use of oral anticoagulants is a risk factor for developing osteoporosis and arterial calcification. A recent animal study demonstrated that high vitamin K intake is capable not only of preventing this calcification to some degree but also of inducing regression of pre-formed arterial calcifications. Trials are planned to further investigate this early finding. Another recent study associated high dietary vitamin K intake with reduced coronary calcification and concluded that adequate intake "could therefore be important to prevent cardiovascular disease." The vitamin K_2 menaquinone was the ester thus associated; the vitamin K_1 ester phylloquinone did not have this positive association.

In a recent prospective cohort study, vitamin K dietary intake was inversely and weakly associated with incidence of prostate cancer. The association noted was between menaquinones and not phylloquinones.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

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

PRECAUTIONS

Those taking warfarin should avoid supplementation with vitamin K unless specifically prescribed by their physicians.

Pregnant women and nursing mothers should avoid supplemental intakes of vitamin K greater than RDA amounts (65 micrograms daily) unless higher amounts are prescribed by their physicians.

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

ADVERSE REACTIONS

The supplemental forms of vitamin K, vitamin K_1 and vitamin K_2 are well tolerated. In one study, doses of 90 milligrams daily of vitamin K_2 were given for 24 weeks. Few adverse effects were noted. Reversible elevations of some liver tests were noted in a few subjects in the study. Menadione (vitamin K_3), which is not used as a nutritional supplemental form of vitamin K for humans, has been reported to cause adverse reactions, including hemolytic anemia.

INTERACTIONS

DRUGS

Broad-Spectrum Antibiotics: Broad-spectrum antibiotics may sterilize the bowel and decrease the vitamin K contribution to the body by the intestinal microflora.

Cephalosporins: Cephalosporins containing side chains of N-methylthiotetrazole (cefmenoxime, cefoperazone, cefotetan, cefamandole, latamoxef) or methylthiadiazole (cefazolin) can cause vitamin K deficiency and hypoprothrombinemia. These cephalosporins are inhibitors of hepatic vitamin K epoxide reductase.

Cholestyramine: Concomitant intake of cholestyramine and vitamin K may reduce the absorption of vitamin K.

Colestipol: Concomitant intake of colestipol and vitamin K may reduce the absorption of vitamin K.

Mineral Oil: Concomitant intake of mineral oil and vitamin K may reduce the absorption of vitamin K.

Orlistat: Orlistat may decrease the absorption of vitamin K.

Salicylates: Salicylates in large doses may inhibit vitamin K epoxide reductase resulting in vitamin K deficiency.

Warfarin: Vitamin K can antagonize the effect of warfarin.

NUTRITIONAL SUPPLEMENTS

Medium Chain Triglycerides: Concomitant intake of medium-chain triglycerides and vitamin K may enhance the absorption of vitamin K.

Squalene: Concomitant intake of squalene and vitamin K may decrease the absorption of vitamin K.

Vitamin A: Intake of high doses of vitamin A may decrease the absorption of vitamin K.

Vitamin E: Intake of very large doses of vitamin E may result in vitamin K deficiency. A vitamin E metabolite, vitamin E quinone, can inhibit vitamin K-dependent gamma-glutamyl carboxylase activity.

FOODS

Olestra: The fat substitute olestra inhibits the absorption of vitamin K as well as the other fat-soluble vitamins A, D and E. These vitamins are added to olestra. Olestra contains 8 micrograms of vitamin K per gram.

DOSAGE AND ADMINISTRATION

There is no typical dosage for vitamin K. Some multivitamin preparations contain vitamin K as vitamin K_1 (phylloquinone or phytonadione) or vitamin K_2 (menaquinones) at doses of 25 to 100 micrograms. The amount of vitamin K in these products is stated as the percentage of the daily value (DV) for vitamin K. The DV is the highest RDA for the vitamin, or 80 micrograms. Vitamin K_1 is also available in 10 milligram doses. In Japan, vitamin K, usually in the form of vitamin K_2, is used for the management of osteoporosis. The fermented soybean product natto is rich in menaquinone-7 or vitamin K_2 ($_{35}$). The bacteria that is used in the preparation of natto, *Bacillus natto*, is also used in Japan as a dietary supplement source of vitamin K_2.

The Food and Nutrition Board of the U.S. National Academy of Sciences has indicated the following Dietary Reference Intakes (DRIs) for vitamin K:

Category	Age (Years)	AI (adequate intake) (micrograms/day)
Infants	0 through 6 months	2.0
	7 through 12 months	2.5
Children	1 through 3 years	30
	4 through 8 years	55
	9 through 13 years	60

Males	14 through 18 years	75
	19 through 30 years	120
	31 through 50 years	120
	51 through 70 years	120
	Older than 70 years	120
Females	14 through 18 years	75
	19 through 30 years	90
	31 through 50 years	90
	51 through 70 years	90
	Older than 70 years	90
Pregnant	18 years or younger	75
	19 through 50 years	90
Lactating	18 years or younger	75
	19 through 50 years	90

The DV (Daily Value) for vitamin K, which is used for determining percentage of nutrient daily values on nutritional supplement and food labels, is 80 micrograms. This is based on the U.S. RDA for vitamin K.

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Wheat Grass/Barley Grass

DESCRIPTION

Cereal grass is the young green plant that grows to produce the cereal grain. Grasses belong to the *Gramineae* family that provides all the world's cereals and most of the world's sugar. Wheat grass and barley grass are popular nutritional supplements. These cereal grasses, along with spirulina (see Spirulina), chlorella (see Chlorella), oat grass and alfalfa are sometimes referred to as "green foods." Wheat grass and barley grass are rich sources of chlorophyll (see Chlorophyll/Chlorophyllin), which is believed to have some health-promoting activities.

ACTIONS AND PHARMACOLOGY

ACTIONS

Wheat grass and barley grass have putative anticarcinogenic activity.

MECHANISM OF ACTION

Wheat sprout extracts have demonstrated antimutagenic activity *in vitro*. The mechanism of the antimutagenic effect is unclear. Wheat sprouts and wheat grass are rich in chlorophyll, and the antimutagenic activity of wheat sprouts may be accounted for by the presence of this substance, which is known to have antimutagenic and anticarcinogenic activities (see Chlorophyll/Chlorophyllin). Other substances, including flavonoids, may also play a role in these possible activities. Barley grass extracts have been found to protect human fibroblasts against carcinogenic agents. Again, chlorophyll may, in part, account for this effect. Barley grass contains several substances other than chlorophyll that have antioxidant activity and that may contribute to its possible antimutagenic and anticarcinogenic activities.

PHARMACOKINETICS

The proteins, lipids and carbohydrates in wheat grass and barley grass are digested, absorbed and metabolized by normal physiological processes.

INDICATIONS AND USAGE

Wheat grass/barley grass supplements are promoted for multiple uses. Claims have been made that they help prevent and fight cancer, lower cholesterol, detoxify many pollutants, protect against solar and other forms of radiation, boost energy and immunity, enhance wound healing, help with digestion, fight tooth decay and bad breath, promote healthy skin, reverse graying of hair and lower blood pressure, among other things. There is no credible evidence to support any of these claims at this time.

RESEARCH SUMMARY

Research is lacking on the possible effects of wheat grass and barley grass. Given that they contain chlorophyll, it is possible that they might have some of the activities exhibited by that substance, including antimutagenic and anticarcinogenic activities. See Chlorophyll/Chlorophyllin.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Wheat grass and barley grass are contraindicated in those who are hypersensitive to any component of a wheat grass- or barley grass-containing supplement.

PRECAUTIONS

Pregnant women and nursing mothers should avoid wheat grass- or barley grass-containing supplements.