SYNONYMS
Vitamin K1 (phytomenadione, phyloquinone, phytonadione), vitamin K2 (menaquinone, MK-4 to MK-14)

DESCRIPTION
It is widely known that vitamin K is essential for coagulation of the blood. In recent years there has been a marked increase in interest in this fat-soluble vitamin due to the discovery of other properties important for health. One important function of vitamin K is the activation of (vitamin K-dependent) enzymes (Gla proteins), which regulate calcium homeostasis (together with vitamin D) and calcification of soft tissues, as well as discouraging decalcification of the bones. There is increasing scientific evidence to suggest that vitamin K serves to counter arterial hardening (sclerosis), bone decalcification, insulin resistance (syndrome) and arthritis, and that it contributes to protection against (cognitive deterioration in) ageing. The current RDA of 75 mcg of vitamin K per day is based on the quantity required for coagulation of the blood, but fails to consider other functions of vitamin K. Research shows that the actual vitamin K requirement is a fair bit higher and that the vitamin K intake of the majority of the population (in the Netherlands) is inadequate.

Vitamin K intake is usually sufficient for haemostasis.

The term vitamin K encompasses a group of related, fat-soluble naphthoquinones. Western foods chiefly contain vitamin K1 (phytomenadione, phyloquinone, phytonadione), which occurs in plants (particularly green tea, algae and green vegetables such as spinach, lettuce, parsley and varieties of cabbage). Vitamin K2 (menaquinone) is produced by certain bacteria and is found to a limited degree in meat, dairy produce and eggs. The gut flora in the large intestine produce vitamin K2, but absorption of this is limited (fat-soluble vitamins are predominantly absorbed in the ileum). There are various forms of menaquinone, MK-4 to MK-14, with the number indicating the quantity of isoprenyl side chains. MK-4 is found in meat and is also produced to a limited extent in the body from vitamin K1. MK-5 to MK-9 are found in small quantities in fermented products such as cheese and yoghurt. The Japanese food nattō (soya beans fermented with Bacillus subtilis) is an exceptionally rich source of MK-7. MK-10 to MK-14 are rare. Vitamin K3 (menadione) is a synthetic (pro)vitamin K. Vitamin K1 and K2 both take care of activation of coagulation factors in the liver. Vitamin K2 is especially active in extrahepatic tissues, in view of the fact that vitamin K1 is mostly absorbed in the liver and less of it ends up in the circulation.

EFFECT
Over fifty years ago it was believed that vitamin K was the only thing necessary for activation (carboxylation) of coagulation factors in the liver. Various extrahepatic vitamin K-dependent Gla proteins have since been discovered. In the bones (and teeth) these include osteocalcin (bone Gla protein, or BGP), protein S and MPG (matrix Gla protein). In the kidneys they include KGP (kidney Gla protein). The vascular wall and other soft tissues contain MPG (matrix Gla protein). The Gla protein Gas6 (growth arrest-specific 6) is a protein produced by (for example) endothelial cells and regulates cell division, cell differentiation and cell migration and protects cells against apoptosis (programmed cell death).

Vitamin K is the cofactor of the enzyme γ-glutamyl carboxylase, which carboxylates glutamic acid (Glu) residues in (vitamin K-dependent) enzymes to form γ-carboxyglutamic acid (Gla) residues, thereby activating them. Undercarboxylated (Glu) proteins are inactive and useless. In vitamin K deficiency, undercarboxylated vitamin K-dependent proteins are in evidence in the blood. These are called PIVKAs (proteins induced by vitamin K deficiency or antagonists). PIVKA-prothrombin (PIVKA-II) is a marker for a serious vitamin K deficiency (vitamin K is primarily used for γ-carboxylation of coagulation factors); undercarboxylated osteocalcin (UcOc or PIVKA-osteocalcin) is a more sensitive marker for vitamin K deficiency. In addition to activating Gla proteins, vitamin K has a variety of other roles.

- **Coagulation**: Vitamin K (K1, K2) is essential for the production of various coagulation factors (Gla proteins) in the liver, including factor II (prothrombin), factor VII (proconvertin), factor IX (thromboplastin component), factor X (Stuart-Prower factor) and proteins C, S and Z. A serious vitamin K deficiency leads to increased coagulation time and raises the chances of excessive haemorrhaging, (occult) blood loss, (subcutaneous) extravasation, wounds that do not heal readily and anaemia.

- **Formation, mineralization and strength of bones**: Osteocalcin is a small, calcium-binding protein chiefly produced by osteoblasts and is a biochemical marker for bone mineralization. It is the most important protein (after collagen) incorporated into the bone matrix during bone formation. Vitamin D encourages the synthesis of osteocalcin and increases the availability of calcium, whilst vitamin K (especially K2) takes care of γ-carboxylation of osteocalcin. Only osteocalcin carboxylated by vitamin K is active and capable of bonding with hydroxyapatite, ensuring calcium deposit in bone tissue. Vitamin K2 not only improves bone quality by activating osteocalcin. In vitro and in vivo studies have shown that vitamin K2 increases the formation and the activity of osteoblasts. It does so by encouraging SXR (steroid and xenobiotic receptor) expression, inhibiting NF-κB and stimulating osteoblast-specific genes. The formation and activity of osteoclasts is reduced by means of inhibition of osteoclastogenesis and induction of their apoptosis, with the expression of cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2).
and various proinflammatory cytokines being inhibited.

- **Inhibition of atherosclerosis**: Carboxylated Matrix Gla Protein (cMGP) plays a central role in the prevention of atherosclerosis by influencing BMP-2 and blocking calcium deposit in the vascular matrix. The production of MGP by (human) vascular smooth muscle cells is stimulated by extracellular calcium (threatening to deposit itself). Activation of MGP is a vitamin K-dependent process. A high serum level of inactive, undercarboxylated MGP (ucMGP) and a high ucMGP/cMGP ratio may be a good marker for (incipient) atherosclerosis. The ucMGP level seems to dip as atherosclerosis progresses, perhaps due to ucMGP bonding with calcium in the vascular wall or loss of smooth muscle cells (owing to apoptosis or transformation into osteoblast-like cells). In addition to activating MGP, vitamin K2 helps keep the blood vessels healthy by lowering the cholesterol level and inhibiting plaque formation (by means of Gas6).

- **Blood glucose regulation**: Vitamin K has a beneficial effect on glucose homeostasis (insulin sensitivity, insulin secretion), in part due to activation of osteocalcin. The precise mechanism of action is as yet unclear; it may be that carboxylated osteocalcin improves insulin sensitivity and beta cell function by improving the expression of adiponectin. It is also possible that vitamin K has a direct impact on insulin sensitivity and glycemic status by means of an anti-inflammatory effect. Furthermore, vitamin K-dependent proteins (prothrombin and protein S) are present in organs important for glucose and insulin metabolism, such as the liver and the pancreas.

- **Inhibiting arthritis**: Vitamin K is an important regulator of bone and cartilage mineralization. In young people vitamin K regulates such things as ossification of epiphyseal plates (plates of cartilage at the ends of the bones allowing for additional growth). There are signs that vitamin K deficiency encourages osteoarthritis due to undercarboxylation of MGP and Gas6 and increasing inflammation (vitamin K inhibits expression of various proinflammatory cytokines). In vitro and animal research is yielding indications that vitamin K2 (MK-4) may have a beneficial effect in rheumatoid arthritis, inhibiting synovial hyperproliferation and, at the right dose, inhibiting the progression of rheumatism.

- **Prevention of arterial stiffness**: As the body ages there is an increase in arterial stiffness. This is caused by the build-up of calcium deposits in the walls of the arteries and this is an independent risk factor for cardiovascular disease. Arterial stiffness increases the risk of arterial wall damage, resulting in narrowing of the arteries caused by a build-up of plaque at an earlier age. A study involving 244 healthy, postmenopausal women aged between 55 and 65 years has revealed that supplementing the diet with vitamin K2 (MK-7) reduces arterial stiffness. After three years, the arterial stiffness in the vitamin K2 group was not only lower, but the flexibility of the arterial wall had even improved. The most significant effect was measured in women who initially had higher levels of arterial stiffness.

- **Role in brain function and synthesis of sphingolipids**: Vitamin K (K1, MK-4) is present in high concentrations in brain tissue and is probably important for brain function. Vitamin K inhibits calcification in soft tissues, activates Gas6 and plays a role in the synthesis of sphingolipids, a group of complex (membrane) lipids that includes cerebrosides, sphingomyelin, sulphatides, ceramides and gangliosides. In laboratory animals vitamin K deficiency produced behavioural changes and a dip in myelin sulphatides in particular. Abnormal sphingolipid metabolism is presumed to play a role in the pathogenesis of age-related disorders, including neurodegenerative diseases, cardiovascular diseases and diabetes. The question is whether vitamin K deficiency contributes to the development and progression of Alzheimer's disease and multiple sclerosis. In laboratory animals low vitamin K intake from birth produced marked cognitive degeneration at an advanced age. In an observational study, people with incipient dementia had a significantly lower intake of vitamin K (on average 63 mcg/day) than healthy people from the same age group (139 mcg/day). In an animal model for multiple sclerosis, preventive vitamin K2 supplements gave rise to a milder course of illness.

- **Anti-inflammatory and antioxidant activity**: In vitro and in vivo research has shown that vitamin K has an anti-inflammatory effect, in part due to inhibition of NF-κB signalling. Moreover, vitamin K has powerful antioxidative properties.

**INDICATIONS**

Vitamin K deficiency: A vitamin K deficiency may be the consequence of insufficient dietary intake of vitamin K, alcoholism, (chronic) liver disease, cystic fibrosis, chronic gastrointestinal diseases (inc. chronic diarrhoea, coeliac disease, Crohn's disease, ulcerative colitis, short bowel syndrome), intestinal resection (especially the last section of the ileum), bariatric surgery (interventions such as gastric banding in cases of morbid obesity) and use of medication (inc. antibiotics, see interactions). Vitamin K particularly accumulates in adipose tissue, and it is possible that people with an elevated percentage of fat (overweight, obesity) have a more significant risk of functional vitamin K deficiency.

Prevention of osteoporosis and bone fractures: Various observational studies have shown a clear (inverse) correlation between vitamin K intake and the chances of bone fractures. Older women with a hip fracture have a significantly lower serum level of vitamin K in comparison with women without a hip fracture. In a study, elderly persons in the highest quartile of vitamin K intake had a 65% lower chance of a hip fracture than elderly persons in the lowest intake quartile. The higher incidence of femur fractures in the west of Japan when compared with other regions shows marked correlation with vitamin K intake. Japanese research demonstrated a significant association between consumption of nattō, which is rich in MK-7, and a reduced chance of a hip fracture in postmenopausal women. A prospective cohort study showed that the UcOc serum level (undercarboxylated osteocalcin) is capable of predicting the chances of a hip fracture in older women, irrespective of the bone mineral density of the femur neck. This was also the conclusion drawn in a 2003 report from the World Health Organization. The connection between undercarboxylated osteocalcin and bone mineral density is rather less clear. Various clinical studies have shown that taking vitamin K2 supplements improves bone quality in cases of osteoporosis by tackling a variety of causes, including oestrogen deficiency (postmenopause), Parkinson's disease, biliary cirrhosis, cirrhosis of the liver, stroke, anorexia nervosa, organ transplantation and use of medicines (see interactions). These studies usually involve use of 45 mcg of vitamin K2 (as MK-4) per day. In Japan, vitamin K2 (45 mcg/day) has regularly been being prescribed for osteoporosis for well over a decade now. In a Canadian study involving 440 women with osteopenia, vitamin K1 (5,000 mcg/day over a period of at least 2 years) significantly reduced the chances of bone fracture in comparison with placebo. The effect of the vitamin K1 is more pronounced if extra vitamin D and calcium are ingested.

In 221 healthy Japanese women (50-70 years of age) a significant inverse association was found between dietary vitamin K intake and UcOc serum levels. The UcOc level also showed a negative correlation with bone mineral density of the lower back. The average vitamin K intake (particularly vitamin K1, because these women hardly ate any nattō) came to 260 mcg/day. Nonetheless, the UcOc levels were...
elevated in 66% of the women, which means that the quantity of vitamin K required for healthy bones far exceeds the current RDA (in the Netherlands) of 75 mcg per day. Researchers estimate that daily intake of 450 mcg of vitamin K (K1/K2) is required to keep bones healthy and that an even higher dose is required to improve bone quality. The elderly need more vitamin K to lower UcOc due to the increased rate of bone turnover.

People with type 2 diabetes are at greater risk of bone fractures, despite a normal or increased bone mineral density (hyperinsulinemia encourages bone mineral density). Vitamin K2 may serve to reduce the chances of bone fractures in diabetics; in an animal model for type 2 diabetes, vitamin K2 supplements resulted in an increase in osteocalcin serum levels, an improvement in (enzymatic) collagen crosslinking, a decrease in (non-enzymatic) collagen crosslinking (such as formation of AGEs, or advanced glycation end products) and an increase in bone strength.

Bone formation in children and adolescents: a great many Dutch children aged 6 to 18 have a higher serum level of undercarboxylated osteocalcin and a greater UcOc/COc ratio than adults, particularly during growth spurts. This indicates that their vitamin K status is substandard and leaves a lot more to be desired than is the case among adults. In a Dutch placebo-controlled study involving 55 healthy prepubescent children, taking vitamin K2 supplements (45 mcg of MK-7 per day over an 8-week period) led to significant improvement of the UcOc/COc ratio and vitamin K status. In healthy girls aged 11 or 12, better vitamin K status is associated with increased bone mineral density. In an observational study involving more than 300 healthy prepubescent children (average age 11.2 years), a better vitamin K status over a period of two years led to a significantly more marked increase in bone mass and overall bone mineral content. Up to around 25 years of age, when peak bone mass (the maximum quantity of bone) is reached, ossification exceeds bone resorption. Thereafter, bone mass gradually decreases. A high peak bone mass reduces the chances of osteoporosis and fractures in later life, and optimum vitamin K status during growth can make a significant contribution in this regard.

Atherosclerosis (arteriosclerotic vascular disease): Sclerosis (hardening) of the arteries is a risk factor for cardiovascular complications, not only in people with existing cardiovascular diseases, diabetes and/or chronic kidney disease but also in asymptomatic individuals. An increase in vitamin K intake contributes to lowering cardiovascular risk, in part by activating MGP. When measurements were taken in a group of healthy Dutch adults, it emerged that a substantial proportion of MGP is inactive, which gives grounds for assuming that many healthy adults have a subclinical vitamin K deficiency. Various observational human studies have found a significant inverse association between vitamin K2 intake (particularly MK-7, MK-8 and MK-9) and the degree of arterial hardening (sclerosis) and the chances of coronary heart disease, myocardial infarction and sudden heart failure. In a Dutch study in which the average intake of vitamin K2 was 31 mcg/day, the chances of coronary heart disease fell by around 9% for each 10 mcg increase in vitamin K2 intake. The use of vitamin K antagonists (anticoagulants such as warfarin) is associated with increased sclerosis of the heart valve and coronary arteries. In an intervention study involving 388 healthy elderly persons, vitamin K1 (500 mcg/day over a period of 3 years) inhibited progression of the hardening of the coronary arteries. Vitamin K2 is more effective than K1 and counters atherosclerosis and cardiovascular diseases at a lower dose. Animal research suggests there is a possibility that vitamin K2 not only inhibits atherosclerosis but also reverses the process. People with chronic kidney disease have a markedly increased chance of developing and dying from cardiovascular diseases, particularly due to increased atherosclerosis (plaque and media sclerosis). In research involving 107 patients with chronic kidney disease it was established that the serum levels of dephosphorylated, undercarboxylated MGP (dp-ucMGP) rise with progression of the kidney disease and that there is a marked positive correlation with the severity of aortic sclerosis. In a pilot study, vitamin K2 lowered dp-ucMGP levels in kidney patients according to the dosage.

Chronic heart failure: The progression of heart failure is characterized by a variety of cellular and molecular processes, including hypertrophy of cardiomyocytes, ventricular enlargement and changes in the extracellular matrix, including fibrosis. This ventricular remodelling is partly down to abnormal regulation of the extracellular matrix; insufficient activity on the part of the vitamin K-dependent matrix Gla protein (due to vitamin K deficiency) may play a role in this. Researchers have ascertained that the plasma level of inactive dp-ucMGP has a marked positive association with the severity of chronic heart failure and the chances of dying from this. The precise function of MGP in the heart has yet to be established, but probably does not relate to prevention of sclerosis. It may be that MGP modulates the activity of growth factors involved in tissue remodelling, such as BMP (bone morphogenic protein), TGFβ (transforming growth factor β) and VEGF (vascular endothelial growth factor). Improvement of vitamin K status might result in a better prognosis in heart failure.

Insulin resistance and diabetes mellitus: various human studies highlight the positive effect of vitamin K on glucose homeostasis. In healthy young adults who underwent a glucose tolerance test, blood glucose levels increased more sharply than they did in test subjects with a low intake of vitamin K. In another experiment, 12 healthy young adults underwent an oral glucose tolerance test twice, the first prior to and the second following a course of vitamin K2 supplements (90 mcg of MK-4 per day over a one-week period). In comparison with the first test, the acute insulin response in the second test was significantly lower in test subjects whose vitamin K status was initially low. In over 2000 Japanese men (65+ years of age), the serum levels of undercarboxylated osteocalcin were inversely associated with plasma glucose levels, haemoglobin A1c levels and degree of insulin resistance (HOMA-IR) where the subject had fasted. In a major prospective cohort study (Framingham Offspring Cohort), a higher intake of vitamin K1 was associated with improved insulin sensitivity and glycaemic status in both men and women. In a Dutch prospective cohort study involving in excess of 38,000 adults who were followed for over a decade, an inverse correlation was found between vitamin K intake (K1 and K2) and the chances of type 2 diabetes. In a clinical study, 355 non-diabetic elderly persons (60-80 years of age) ingested a daily dose of 500 mcg of vitamin K1 or a placebo over a period of 36 months. In men, taking vitamin K supplements resulted in a significant fall in insulin levels and decrease in insulin resistance when fasting.

Osteoarthritis and rheumatoid arthritis: In a prospective observational cohort study, the Framingham Offspring Study, involving 673 elderly persons, an inverse correlation was found between vitamin K1 plasma levels and the chances of osteoarthritis, osteophyte formation and narrowing of the interarticular space (hand, knee). Intervention studies will have to shed light on whether improving vitamin K status has an effect on the disease process. The role of vitamin K2 in rheumatoid arthritis has not yet been studied in humans.
CONTRA-INDICATIONS
In the case of individuals taking anticoagulants (vitamin K antagonists), a supplement that supplies a dose of more than 100 mcg of vitamin K per day should only be used under medical supervision. Vitamin K is contraindicated in those who are hypersensitive or allergic to this vitamin (rare).

SIDE EFFECTS
Vitamin K1 and vitamin K2 do not have any toxic effects. Toxicological research has not managed to establish an upper limit for intake. In animal subjects a one-off oral dose of 25,000 mcg/kg (25,000,000 mcg/kg) was not fatal; neither were any harmful effects observed following a daily dose of 2,000 mcg (2,000,000 mcg) of vitamin K per kilogram of body weight over a period of 30 days. Excessive intake of vitamin K during pregnancy (particularly the synthetic K3 variant) increases the risk of jaundice in the newborn child and should be avoided. Intake of vitamin K during breastfeeding is safe.

INTERACTIONS
- Various medicines lower vitamin K status: antibiotics decrease endogenous vitamin K2 synthesis due to their negative effect on intestinal flora; bile acid sequestrants (cholestyramine, colestipol) inhibit uptake of fat-soluble nutrients, including vitamin K; corticosteroids increase excretion of vitamin K via the urine; anticonvulsants (inc. phenytoin, phenobarbital) increase the breakdown of vitamin K in the liver; salicylates (aspirin) lower vitamin K status.
- Taking vitamin K supplements reduces the effectiveness of vitamin K antagonists. Use of this medication requires medical supervision where daily intake of vitamin K exceeds 100 mcg.
- Vitamin A and vitamin E can lower vitamin K status (particularly at high doses).

DOSEAGE
The RDA (in the Netherlands) for vitamin K (K1/K2) is 75 mcg (1-1.5 mcg/kg/day) for adults (35 mcg/day for children, 75 mcg/day for adolescents). The United States recommends an AI (Adequate Intake) for adult men and women of 120 and 90 mcg per day respectively. Shortly after birth, babies are given an extra shot of vitamin K (1,000 mcg) and breastfeeding mothers are advised to give their baby a daily dose of 150 mcg of vitamin K1 from the first 3 months in order to prevent haemorrhaging due to vitamin K deficiency.

Taking the (Dutch) RDA as a premise, most adults in the Netherlands are ingesting sufficient quantities of vitamin K; median intake is around 100 mcg/day, 10% of which is vitamin K2. People who eat plenty of vegetables are capable of reaching 250 mcg/day. However, adequate intake of vitamin K, providing maximum carboxylation of (extrahepatic) vitamin K-dependent proteins, is estimated to be 400-1000 mcg of vitamin K (K1/K2) per day for healthy adults. This implies that vitamin K intake is too low among the majority of the adult population in the Netherlands.

Vitamin K intake is better in countries such as China and Japan (around 240 mcg/day), where vitamin K2 (MK-7) constitutes a much higher proportion of vitamin K intake. In comparison to vitamin K1, vitamin K2 is more readily absorbed, results in higher and more stable plasma levels of vitamin K, has a considerably longer half-life (3 days versus 2 hours) and is more readily absorbed into extrahepatic tissues. With regard to lowering UcOc (for example), a dose of 45 mcg of MK-7 corresponds to around 120 mcg of vitamin K1.

When taking vitamin K supplements, daily doses varying from 45 mcg (vitamin K2) to 10,000 mcg (vitamin K1) are used. The British Expert Group on Vitamins and Minerals (EVM) proposes a general therapeutic dose of 1,000 mcg of vitamin K1 per day (or 20 mcg/kg /day).

SYNERGISM
- Vitamin D boosts the effects of vitamin K against such conditions as osteoporosis and atherosclerosis.

REFERENCES


- Tolerable upper intake levels for vitamins and minerals. Parma: European Food Safety Authority; 2006.


