

Introduction

In 1929 Henrik Dam observed that chicks fed on fat-free diets developed haemorrhages and started bleeding. In 1935 he proposed that the antihaemorrhagic substance was a new fat-soluble vitamin, which he called vitamin K (after the first letter of the German word “Koagulation”). Vitamin K is indeed fat-soluble, and it occurs naturally in two forms: vitamin K₁ (phylloquinone) is found in plants; vitamin K₂ is the term for a group of compounds called menaquinones (MK-n, n being the number of isoprenyl units in the side chain of the molecule) which are synthesised by bacteria in the intestinal tract of humans and various animals. Vitamin K₃ (menadione) is a synthetic compound that can be converted to K₁ in the intestinal tract. It is only used in animal nutrition.

Functions

Vitamin K is essential for the synthesis of the biologically active forms of a range of proteins called vitamin K-dependent proteins. Vitamin K participates in the conversion of glutamate residues of these proteins to γ -carboxylglutamate residues by addition of a carboxyl-group (carboxylation).

In the absence of vitamin K, carboxylation of these proteins is incomplete, and they are secreted in plasma in various so called under-carboxylated forms, which are biologically inactive.

Vitamin K is also essential for the functioning of several proteins involved in blood coagulation (clotting), a mechanism that prevents bleeding to death from cuts and wounds, as well as internal bleeding.

Vitamin K-dependent proteins:

- Prothrombin (factor II), factors VII, IX, and X, and proteins C, S and Z are proteins that are involved in the regulation of blood coagulation. They are synthesised in the liver. Protein S has also been detected in bone.
- The vitamin K-dependent proteins osteocalcin and MGP (matrix Gla-protein) have been found in bone. Osteocalcin is thought to be related to bone mineralisation. Matrix Gla-protein is present in bone, cartilage and vessel walls and has recently been established as an inhibitor of calcification. The role of protein S in bone metabolism is not clear.
- Recently, several other vitamin K-dependent proteins have been identified.

Main functions in a nutshell:

- Coenzyme for a vitamin K-dependent carboxylase
- Blood coagulation
- Bone metabolism

Dietary sources

The best dietary sources of vitamin K₁ are green leafy vegetables such as spinach, broccoli, Brussels sprouts, cabbage and lettuce. Other rich sources are certain vegetable oils. Good sources include oats, potatoes, tomatoes, asparagus and butter. Lower levels are found in beef, pork, ham, milk, carrots, corn, most fruits and many other vegetables.

An important source of vitamin K₂ is the bacterial flora in the anterior part of the gut – the jejunum and ileum.

Vitamin K content of foods

Food	Vitamin K (µg/100g)
Spinach	305
Brussels sprouts	236
Broccoli	155
Rape seed oil	150
Soya bean oil	138
Lettuce	109
Cabbage	66
Asparagus	39
Olive oil	33
Butter	7

(Souci, Fachmann, Kraut)





Absorption and body stores

Vitamin K is absorbed from the jejunum and ileum. As with other fat-soluble vitamins, absorption depends on the presence of bile and pancreatic juices and is enhanced by dietary fat. Although the liver is the main storage site, vitamin K is also found in extrahepatic tissues, e.g. bone and heart. Liver stores consist of about 10% phyloquinones and 90% menaquinones. Compared with that of other fat-soluble vitamins, the total body pool of vitamin K is small and turnover of vitamin K in the liver is rapid. The body recycles vitamin K in a process called the vitamin K cycle, allowing the vitamin to function in the γ -carboxylation of proteins many times over.

Although the liver contains menaquinones synthesised by intestinal bacteria, the absorption of menaquinones and their contribution to the human vitamin K requirement have not yet been fully elucidated.

Measurement

Plasma vitamin K concentration is measured by high performance liquid chromatography. The normal range of plasma vitamin K in adults is 0.2-3.2 ng/ml. Levels below 0.5 ng/ml have been associated with impaired blood-clotting functions. However, the value of measuring plasma vitamin K concentration to assess vitamin K status is limited because it responds to changes in

dietary intake within 24 hours.

Overt vitamin K deficiency results in impaired blood clotting, usually demonstrated by laboratory tests that measure clotting time.

Plasma concentration of one of the vitamin K-dependent blood-clotting factors – prothrombin, factor VII, factor IX or factor X – is measured to assess an inadequate intake of vitamin K. The normal range of plasma prothrombin concentration is from 80 to 120 μ g/ml.

Recently, other parameters for assessing vitamin K status have been studied, e.g. measurements of undercarboxylated prothrombin and undercarboxylated osteocalcin in both normal and pathological conditions.

Stability

Vitamin K compounds are moderately stable to heat and reducing agents, but are sensitive to acid, alkali, light and oxidising agents.

Interactions

Negative interactions

- Coumarin anticoagulants (such as warfarin), salicylates and certain antibiotics act as vitamin K antagonists.
- Very high dietary or supplemental intakes of vitamin K may inhibit the anticoagulant effect of vitamin K antagonists (e.g. warfarin).
- High doses of vitamins A and E have been shown to interfere with vitamin K and precipitate deficiency states.
- Absorption of vitamin K may be decreased by mineral oil, bile acid sequestrants (cholestyramine, colestipol) and orlistat (weight loss medication).

Deficiency

Vitamin K deficiency is uncommon in healthy adults but occurs in individuals with gastrointestinal disorders, fat malabsorption or liver disease, or after prolonged antibiotic therapy coupled with compromised dietary intake. Impaired blood clotting is the clinical symptom of vitamin K deficiency, which is demonstrated by measuring clotting time. In severe cases, bleeding occurs. Adults at risk of vitamin K deficiency also include patients taking anticoagulant drugs which are vitamin K antagonists.

Newborn infants have a well established risk of vitamin K deficiency, which may result in fatal intracranial haemorrhage (bleeding within the skull) in the first weeks of life. Breast-fed infants in particular have a low vitamin K status because placental transfer of vitamin K is poor and human milk contains low levels of vitamin K. The concentrations of plasma clotting factors are low in infants due to immaturity of the liver. Haemorrhagic disease in the newborn is a significant worldwide cause of infant morbidity and mortality. Therefore, in many countries vitamin K is routinely administered prophylactically to all newborns.

Disease prevention and therapeutic use

Phylloquinone is the preferred form of the vitamin for clinical use. It is used for intravenous and intramuscular injections as a colloidal suspension, emulsion or aqueous suspension, and as a tablet for oral use. Vitamin K₁ is used in the treatment of hypoprothrombinemia (low amounts of prothrombin), secondary to factors limiting absorption or syn-

thesis of vitamin K. During operations in which bleeding is expected to be a problem, for example, in gallbladder surgery, vitamin K₁ is administered.

Anticoagulants inhibit vitamin K recycling, which can be corrected rapidly and effectively by the administration of vitamin K₁.

Vitamin K₁ is often given to mothers before delivery and to newborn infants to protect against intracranial haemorrhage.

A putative role of vitamin K in osteoporosis has been investigated since vitamin K-dependent proteins have been discovered in bone. However, further investigations are required to resolve whether vitamin K is a significant etiological component of osteoporosis. A role for vitamin K in the development of atherosclerosis is also under discussion, but studies supporting this hypothesis are limited and future research is recommended.

Recently, studies with cancer cell lines and animal studies have indicated that a combination of vitamin C and vitamin K₃ has antitumor activity and inhibits the development of metastases.

Recommended Daily Allowance (RDA)

The US Food and Nutrition Board of the Institute of Medicine (2001) has established an adequate intake (AI) level for adults based on reported dietary intakes of vitamin K in apparently healthy population groups. Other health authorities have come to similar conclusions.

Safety

Even when large amounts of vitamin K₁ and K₂ are ingested over an extended period, toxic manifestations have not been observed. Therefore, the major health authorities have not established a tolerable upper level of intake (UL) for vitamin K. Allergic reactions have been reported, however. Furthermore, administered menadione (K₃) has been known to cause haemolytic anaemia, jaundice and kernicterus (a grave form of jaundice in the newborn) and is no longer used for treatment of vitamin K deficiency.

Supplements, food fortification and other applications

Supplements of vitamin K are available alone in tablets and capsules, and also in multivitamin preparations.

Infant formula products, beverages and cookies are fortified with vitamin K. Menadione salts are generally preferred for farm animals because of their stability.

Industrial production

The procedure involves the use of monoester, menadiol and an acid catalyst. Purification of the desired product to remove unreacted reagents and side products occurs either at the quinol stage or after oxidation.

Current recommendations in the USA

RDA*

Infants	< 6 months	2 µg (AI)
Infants	7-12 months	2.5 µg (AI)
Children	1-3 years	30 µg (AI)
Children	4-8 years	55 µg (AI)
Children	9-13 years	60 µg (AI)
Children	14-18 years	75 µg (AI)
Males	> 19 years	120 µg (AI)
Females	> 19 years	90 µg (AI)
Pregnancy	14-18 years	75 µg (AI)
Pregnancy	> 19 years	90 µg (AI)
Lactation	14-18 years	75 µg (AI)
Lactation	> 19 years	90 µg (AI)

*The Dietary Reference Intakes (DRIs) are actually a set of four reference values: Estimated Average Requirements (EAR), Recommended Dietary Allowances (RDA), Adequate Intakes (AI), and Tolerable Upper Intake Levels, (UL) that have replaced the 1989 Recommended Dietary

Allowances (RDAs). The RDA was established as a nutritional norm for planning and assessing dietary intake, and represents intake levels of essential nutrients considered to meet adequately the known needs of practically all healthy people

History

- 1929** A series of experiments by Dam results in the discovery of vitamin K.
- 1931** A clotting defect is observed by McFarlane and coworkers.
- 1935** Dam proposes that the antihæmorrhagic vitamin in chicks is a new fat-soluble vitamin, which he calls vitamin K.
- 1936** Dam and associates succeed in preparing a crude plasma prothrombin fraction, and demonstrate that its activity is decreased when it is obtained from vitamin K-deficient chick plasma.
- 1939** Vitamin K₁ is synthesised by Doisy and associates.
- 1940** Brikhous observes hæmorrhagic conditions resulting from malabsorption syndromes or starvation, and finds that hæmorrhagic disease of the newborn responds to vitamin K.
- 1943** Dam receives half of the Nobel prize for his discovery of vitamin K, the blood coagulation factor.
- 1943** Doisy receives half of the Nobel prize for his discovery of the chemical nature of vitamin K.
- 1974** The vitamin K-dependent step in prothrombin synthesis is demonstrated by Stenflo and associates and Nelsestuen and colleagues.
- 1975** Esmon discovers a vitamin K-dependent protein carboxylation in the liver.



Carl P. H. Dam



Edward A. Doisy