Vitamin K

https://open-global.kcl.ac.uk/vitamin-k/

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Importance of vitamin K for health

Vitamin K is essential for normal blood coagulation; it functions as a co-enzyme during the synthesis of several proteins involved in coagulation. Importantly, these proteins include prothrombin (also known as coagulation Factor II). In individuals with vitamin K deficiency, the "prothrombin time" increases, and in severe cases can lead to haemorrhage (1). Vitamin K is also important in bone metabolism.

Vitamin K occurs in several different forms, but all share the menadione ring structure (2-naphthoquinone). Phylloquinone (2-methyl-3-phytyl-1,4-naphthoquinone), known as vitamin K_1, is found in all green vegetables such as spinach, broccoli, kale and Swiss Chard, which contain >200 μg/100 g (2, 3). Bioavailability in green vegetables is low (<10%). Some fat consumed concomitantly helps the absorption of the vitamin in the digestive tract. Soybean and canola oil are also sources of vitamin K (100 μg/ 100 g) with a higher bioavailability (2), though these oils are likely consumed in lesser quantities than green leafy vegetables, bringing the overall contribution relatively similar.

The second form of vitamin K, the menaquinones, collectively known as vitamin K_2, have a long chain with 6 to 13 isoprenoid units in the 3-position, and are denoted by MK-*n*, where *n* signifies the number of isoprenoid units (4-6). Menaquinones are produced by bacterial fermentation, either in the large intestine (mainly by *Bacteriodes spp.*), or in foods such as cheese, curd and natto, a Japanese food made of fermented soya beans (3-6). Menaquinones have a different bioavailability – almost 100% from dairy produce (6, 7). They also have different pharmacokinetics to phylloquinones, leading to variable plasma half-life times (4) and distrubution. Menaquinones produced by intestinal bacterial are, however, poorly available for intestinal absorption (8). The composition of menaquinone intake varies regionally, depending on the type of produce being consumed in the habitual diet (9) and may be a relatively small contributor to total vitamin K intake.

MK-4 is different to other menaquinones, in that it is not a major bacterial product, but is formed by the cellular alkylation of Vitamin K_3 (menadione; 2-methoyl-1,4-naphthoquinine), which is a synthetic form of vitamin K found in animal feed and thus originates from animal products, or from phylloquinone, with menadione as intermediate (4).

Risk and consequences of vitamin K deficiency

Due to dietary ubiquity and recycling of the vitamin K molecule, vitamin K deficiency is rare in adults, and mainly limited to those with disorders of fat absorption and digestion (2). However, low vitamin K intakes are associated with an increased risk of osteoporotic fractures (2) and are associated with a higher risk of cardiovascular disease , though data from clinical trials on the beneficial role of vitamin K do not support supplementation (3).

Vitamin K deficiency is much more frequent in neonates than in adults, since infants are born vitamin K-deficient due to poor maternal-placental transfer (2), and a low endogenous production due to a sterile gut (8).

WHO recommendation (2018): *All newborns should be given 1 mg of vitamin K intramuscularly after birth [after the first hour during which the infant should be in skin-to-skin contact with the mother and breastfeeding should be initiated]. (Strong recommendation, moderate quality evidence.) See* https://extranet.who.int/rhl/topics/newborn-health/care-newborn-infant/who-recommendation-haemorrhagic-disease-prophylaxis-using-vitamin-k

Risks of vitamin K excess

Vitamin K is not toxic, and there is no upper limit within current dietary reference intakes (2).

Human biomarkers of population vitamin K status

To date, population surveys including assessment of vitamin K intake have relied on dietary intake and food frequency questionnaires, however the data generated are inconsistent (9).

Biomarkers of vitamin K status have been reviewed in (3). There is currently no single biomarker of vitamin K status for use in population studies (3, 9), and data are complex to interpret (3). Of the available biomarkers of vitamin K activity, whilst they respond to phylloquinone repletion following a period of depletion there are none for which a dose-response relationship with phylloquinone intake has been firmly established (3).

Circulating vitamin K can be measured in serum/plasma as phylloquinone, and most available data are related to phylloquinone (3).

Phylloquinone is readily detected in the circulation, and levels respond to intake, however the relatively short half-life (10) means that circulating concentrations reflect recent intake only (9), and no cut-off values to determine adequate vitamin K status are, to date, available (3).

Because of their strong association consideration should be given to the adjustment of plasma phyllooquinone concentration relative to triacylglyceride concentration (3).

Methods: **HPLC with fluorescence detection and LC-mass spectrometry**, on fasting blood samples. See SOP available on page 3 of www.open-global.kcl.ac.uk/vitamin-k/

Sample type: Phylloquinone may be measured in plasma or serum.

Quality control: Analytical procedures should be performed under subdued lighting and samples stored at <20°C.

Other methods:

The menanoquinones can be measured by HPLC but circulating concentrations are generally much lower than phylloquinone except in specific population groups or in people taking menaquinone-containing supplements and thus have not been adopted for population assessment (9).

Undercarboxylated vitamin K-dependent proteins can be measured to assess vitamin K status. When vitamin K is insufficient, the post-translational carboxylation of vitamin K-dependent proteins, such as prothrombin, is reduced. The undercarboxylated (inactive) fraction rises and can be detected.

Undercarboxylated prothrombin, PIVKA-II, is measureable in circulation, however is not used as a population biomarker as the commercially-available kits have a low sensitivity in detecting variation, except in individuals with chronic kidney disease (9). It is most often used in clinical settings.

Osteoalcin: An alternative is to measure osteocalcin, a vitamin K dependent protein synthesised uniquely during bone formation. Osteocalcin is detectable in serum, and the undercarboxylated

portion of the protein is responsive to changes in vitamin K intake (9). It is thought to be a more sensitive indicator for individuals in the community than PIVKA-II (9). Osteocalcin is measured by immunoassay or mass spectrometry (9).

Urinary biomarkers of vitamin K status are available, which measure urinary γ-carboxyglutamic acid (Gla) and menadione, but these are yet restricted to a clinic setting, since 24h urine collection is required (9).

Prothrombin time is the only vitamin K biomarker for which a change (increase) has been associated with vitamin K deficiency (3). It is used in a clinical setting.

Accreditation schemes

KEQAS: Vitamin K External Quality Assurance Scheme

https://www.guysandstthomas.nhs.uk/our-services/human-nutristasis/vitkeqas.aspx

This scheme assures the quality of laboratory measurements of phylloquinone, Vitamin K_1, with the intention of harmonisation of methods for vitamin K analysis and their application to nutritional and clinical studies.

Participating laboratories receive four batches of three samples annually and are required to analyse them during specific periods over the course of the year. When results are returned, they are subjected to statistical analysis including an outliers test and a Z scoring system. Members then receive comprehensive reports detailing their performance.

KEQAS is a UKNEQAS affiliated EQA scheme. Viapath Analytics LLP, operating KEQAS, is a UKAS accredited proficiency testing provider (No. 7586).

Laboratories interested in participating in the KEQAS scheme should contact David Card (david.card@viapath.co.uk)

Join the KEQAS LinkedIn group: https://www.linkedin.com/groups/2675928/about

KEQAS provide technical advice for users of the supported laboratory methods. Contact david.card@viapath.co.uk

For further information, contact the OpeN-Global team via www.open-global.kcl.ac.uk/contact/

Useful links

European Food Safety Authority (EFSA) Dietary reference values for vitamin K:
https://www.efsa.europa.eu/en/efsajournal/pub/4780

NIH Factsheet for Health Professionals: Vitamin K https://ods.od.nih.gov/factsheets/VitaminK-HealthProfessional/

Further reading

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