

Review article - Impact of Vitamin K on Human Health**Najwan K. Fakhree*¹, Sarah H. Mhaibes* and Heba H. Khalil***

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Abstract

Vitamin K is an important fat-soluble vitamin that naturally occurs as 2 types; vitamin K1 (phylloquinone, PK) and vitamin K2 (menaquinones, MKs). Vitamin K is necessary for blood clotting as it plays a crucial role in the synthesizing of blood clotting proteins in the liver. The deficiency of vitamin K is rarely occurs however, some groups of people such as elderly and people with intestinal absorption impairment can find it difficult to get adequate vitamin K. Recently the interest for vitamin K influence on human health apart from its clotting effect has increased and several studies reported that chronic subclinical deficiency of vitamin K may be a risk factor for many diseases such as osteoporosis, atherosclerosis, cancer, insulin resistance, neurodegenerative diseases and others. The aim of this review is to clarify the role of vitamin K in preventing and treating different aspects of human diseases.

Keywords: Vitamin k, Sources of vitamin k, Pharmacokinetics of vitamin k, Safety and toxicity of vitamin k.**تأثير فيتامين ك على صحة الانسان**نجوان قيصر فخري*¹، سارة هاشم محببس* و هبة هاشم خليل*

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الخلاصة

فيتامين ك هو احد الفيتامينات المهمة الذائبة في الدهون والذي يوجد طبيعياً على نوعين فيتامين ك 1 و فيتامين ك 2. إن فيتامين ك ضروري في عملية تخثر الدم حيث يلعب دور أساسي في تصنيع بروتينات تخثر الدم في الكبد. على الرغم من أن العوز في فيتامين ك نادر الحدوث لكن بعض المجاميع من الأشخاص مثل كبار السن والأشخاص الذين لديهم إعاقة في الامتصاص المعوي توجد لديهم صعوبة في الحصول على كمية كافية من فيتامين ك. حديثاً زاد الاهتمام حول تأثير فيتامين ك على صحة الإنسان بجانب تأثيره على التخثر حيث أشارت العديد من الدراسات إلى أن العوز المزمن تحت السريري لفيتامين ك ممكن أن يشكل عامل خطورة للعديد من الأمراض مثل هشاشة العظام، تصلب الشرايين، السرطان، مقاومة الأنسولين، الأمراض العصبية التنكسية وغيرها. إن الهدف من هذه المراجعة هو لتوضيح دور فيتامين ك في منع حدوث ومعالجة العديد من الأمراض في الإنسان.

الكلمات المفتاحية: فيتامين ك، مصادر فيتامين ك، حركة فيتامين ك، سلامة وسمية فيتامين ك.**Introduction**

Vitamin K is a fat-soluble vitamin necessary for blood coagulation. The vitamin was discovered by Danish research scientist Henrik Dam in Germany in 1929 and was called "K" since the earliest discoveries were published in a German journal, in which the substance was referred to as the "Koagulation vitamin."

The pure vitamin (K1) was derived from alfalfa in 1939 and it was subsequently realized that a second form (K2) with the more unsaturated side chain was synthesized by the bacteria⁽¹⁾.

Vitamin K1 and vitamin K2 occur naturally, and are primarily present in vegetables with green leaves. They absorbed from the small intestine. The quantity of fat in the diet and the production of bile acid in the liver are essential for absorption. Similar to other lipid soluble vitamins, vitamins K1 and K2 are initially spread in chylomicrons (CMs) that go into the circulation via lymphatics.

The synthetic type of vitamin k (vitamin K3) is soluble in water and absorbed in the lack of bile

acids, directly moving from the mucosal cells of the intestine into the liver portal blood⁽²⁾.

Liver consider as the storing of vitamin K. Vitamin K is essential for hepatic post synthetic activation of coagulation factor II (prothrombin), VII, IX and X, in addition to anti-coagulant protein C and S, Initially, all are synthesized as non-active precursor proteins by the liver. Thus, vitamin k deficiency extends the clotting time. Vitamin k deficiency is usually caused by abnormal absorption rather than in the lack of vitamin in food. Vitamin K has an essential role for numerous physiological processes as the sole cofactor of γ -glutamyl carboxylase enzyme (GGCX) that catalyzed post translational shift, which lead to Vitamin K-dependent proteins (VKDPs) activation engaged in the formation of bone, tumor growth prevention, inflammatory reactions and several other biologically important function⁽³⁾. The goal for this review is to clarify the function of vitamin K in preventing and treating different aspects of human diseases.

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Types and Sources of Vitamin K

There are 3 different vitamin K types: K1 obtained from plants; K2 produced by bacteria or fermentation; and K3 produced synthetically^(4,5). Vitamin K naturally occurs as vitamin K1 (phyloquinone, PK) and as vitamin K2 (including several various vitamins, known as menaquinones, MKs). Menaquinones (vitamin K2) are a subfamily with a length of 1 to 13 isoprene residues in the lateral chain that are all unsaturated. Different menaquinones are commonly referred to as MK-n, where n means the number of the aliphatic side chain isoprene residues. Relevant menaquinones include the short chain MK-4, the only MK which formed by a systemically conversion of PK into MK, and the long chain of menaquinones MK-7, MK-8, MK-9 and MK-10, all of which are present in human nutrition while little amounts of MK-6 are contained in different foodstuffs. Vitamin K1 is found chiefly in green leafy foods like broccoli, kale and spinach. Its viscous oil; yellow color, dissolve in vegetable

oil, it is also found in fruit such as avocado, kiwi and grape as well as olive oil and soy oil. Vitamin K1 is called phyloquinone since it is a photosynthesis indirectly found in plant leaves where it occurs in chloroplasts and takes part in the 1 photosynthetic procedure. Fascinatingly vitamin K1 is especially sensitive to sunlight (1 hour of exposure destroyed it). Although the source of vitamin K2 (menaquinones) seems to be more unclear and while the involvement of bacterial flora in small intestine to vitamin K is still incomprehensible, menaquinones are mainly derived from bacterial flora but the amount of vitamin K2 produced is considered to be minimal. K2 also present in fermented foods (e.g. cheese and the Japanese soy product 'Natto')^(6,7). Furthermore, there is a synthesized form of vitamin K: menadion, or vitamin K3(2-methyl-1,4-naphthoquinone nucleus), which is a structural precursor to vitamins K1 and K2. Menadion supplement is prohibited by FDA due to its toxicity⁽⁵⁾ (Figure 1, Table 1);

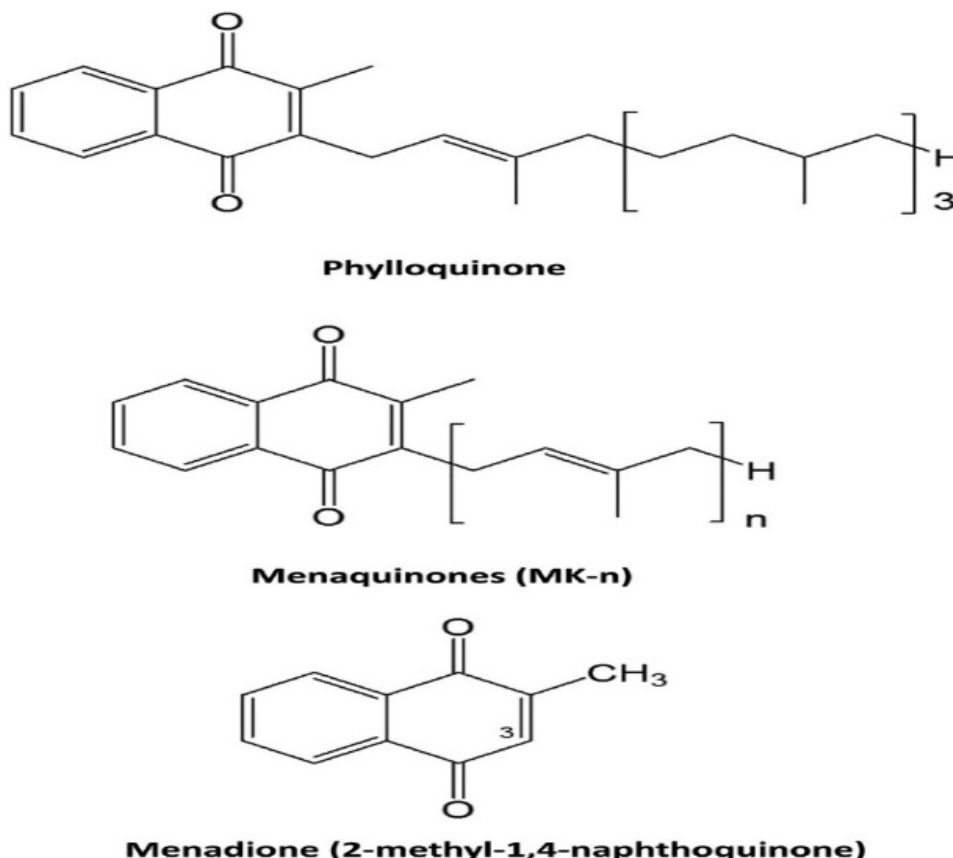


Figure 1. Structure of vitamin K1 (phyloquinone) and vitamin K₂(menaquinone) Menadion (vitamin K₃) represent the common K1 and K2 structure Menadione is a synthetic vitamin K type.⁽⁶⁾

Table 1. Vitamins k types, sources and function ⁽⁷⁾

Type of vitamin K	Sources of vitamin K	Function in the human body
Vitamin K1	Green leafy vegetables and some plant oils.	Takes part in blood coagulation as an enzyme cofactor which catalyzes carboxylation (insertion of a carboxy group-COOH) of some glutamic acid residues to gamma-carboxyglutamate (Gla). Factors II, VII, IX and X contain GLa protein.
Vitamin K2, menaquinones-4 (MK-4)	(I) Butter, egg yolks, pork fat and Nutrition based on animals. (II) Synthesized by bacteria flora in the intestine (however, synthesized MK-4 is attached to the bacteria membranes in the intestine and Small amount in humans is absorbed). (III) Over-the-counter (OTC) medicines	(I) Osteocalcin (which is synthesized in bones) (II) Matrix GLa protein (synthesized in cartilage and in the walls of blood vessel) it is implicated in the transportation of calcium, Hindering the accumulation of calcium in the walls of blood vessel, and helps to increase the density of the bone. (III) MK-4 is Short chain type with shorter half-life.
Vitamin K2, menaquinone-7 (MK-7)	(I) Certain types of cheese and fermented foods, extracted from Natto (fermented soy) (II) Extracted from Natto (fermented soy) as OTC medicines	Function of MK-7 like MK-4 .MK-7 is Long chain type with longer half-life.
Vitamin K3, menadione.	Synthetic form of vitamin K considered a provitamin.	(I) Has been prohibited in the USA by the FDA due to possible toxicity (hemolytic anemia). (II) It recently being investigated as a possible therapy for prostate / hepatocellular cancer and treatment option for the toxicity of skin secondary to kinase inhibitor medication.

Pharmacokinetics of Vitamin K

Like other lipid-soluble vitamins, vitamin K is mainly absorbed in the proximal intestine. After the absorption, vitamin K emulsified into mixed micelles via bile salts and incorporated into the apoA- and apoB-48-containing chylomicrons (CMs). CM is then secreted into the lymph and goes to blood through lacteals and thoracic ducts. CMs in)

the blood are hydrolysed via lipoprotein lipase on the capillary of endothelial cells surface. After clearance of triglyceride core, chylomicron remnant (CR) which is smaller CM residues will be produced and circulation will resume after loss most of apoC and apoA, but vitamin K retained in the lipophilic core ⁽⁸⁾. (Figure2

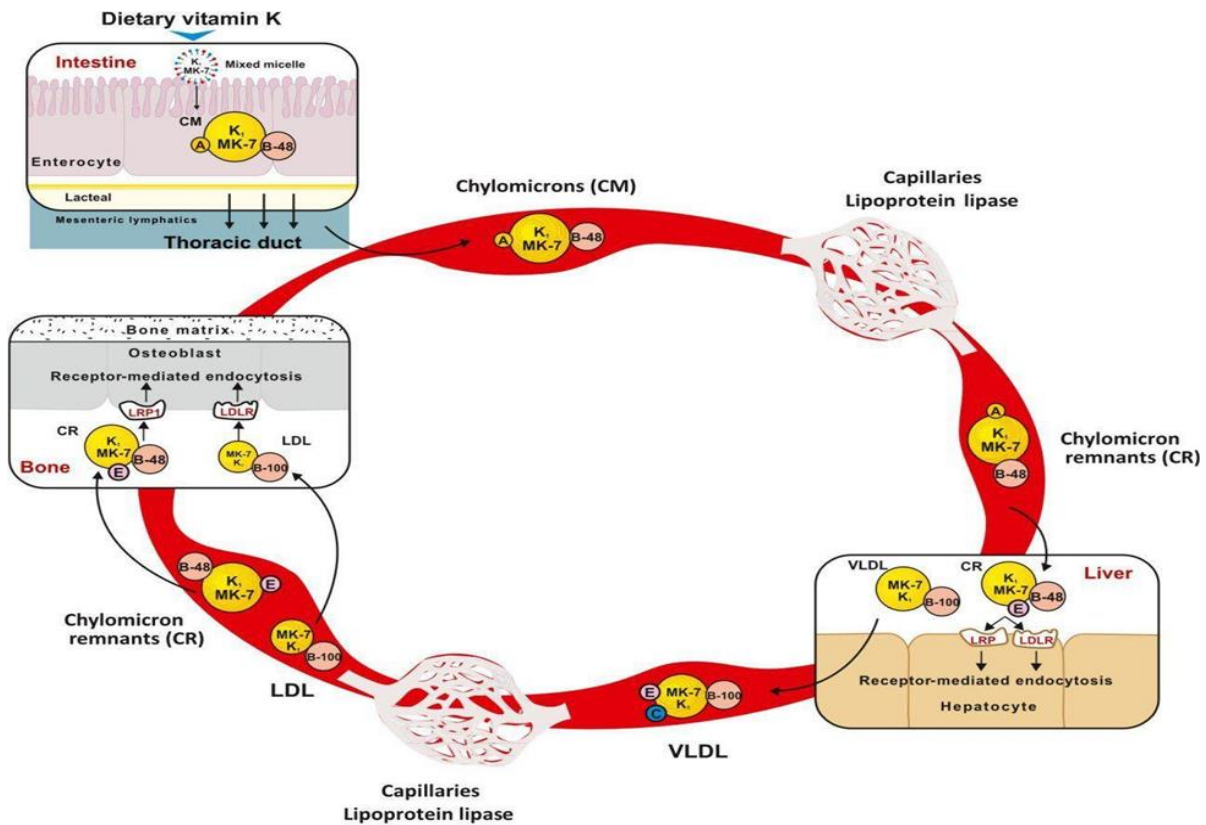


Figure 2. Schematic diagram of dietary phylloquinone (K1) and menaquinone-7 (MK-7) absorption, transportation, and cellular uptake ⁽⁸⁾.

Uptake of vitamin K by liver

In liver CR the classical endocytotic receptor pathway via the low density lipoprotein receptor (LDLR) and receptor-related protein 1 (LRP) is observed. The lipids incorporated into VLDL with apoB-100 and revert to blood where apoE and apoC are acquired. The consequent hydrolysis of triglycerides within capillaries produces VLDL residues known as intermediate-density lipoproteins (IDL) and releases free fatty acids. Additional changes to IDL include reduction of apoE and apoC and. This way allows the remaining VLDL particles to be converted to LDL. Vitamin K is still supposed to be in the lipophilic core ⁽⁸⁾. (Figure 2)

Uptake of vitamin K by bone

Nutritional vitamin K is supplied by circulating lipoproteins like CR and LDL to the human bone. The LRPI and LDLR are expressed by osteoblasts. Study of vitamin K absorption has shown that most osteoblasts obtain phylloquinone by CR way and MK-7 through LDL way ⁽⁸⁾.

Excretion of vitamin K

Vitamin K is metabolized in the liver and excreted in the urine and bile mainly in the form of glucuronide conjugates of two major carboxylic aglycones, with 5-7C side chains, respectively. In study with radio-labeled phylloquinone, 20% of the injected dose was excreted into the urine, while 40%

were excreted through the bile in the feces; the proportion was identical despite of either the dose injected is 1-45 mg. There were no equivalent excretion data for menaquinones ⁽⁸⁾.

Mechanism of action of vitamin k

The mechanism of action of vitamin K is to add a functional carboxylic acid group to a protein amino acid glutamate (Glu) residue, to form a gamma carboxyglutamate (Gla). This unusual post-translation alteration of the protein, referred as the "Gla-protein". Within the gamma-carboxyglutamate residue, the existence of two -COOH (carboxyl acid) groups on the same carbon enables it to chelating calcium ions. This way the binding of calcium ions most often affects the action or binding of Gla-protein enzymes, like that of the vitamin K-dependent coagulation factors. Vitamin K is reduced in the cell to a reduced form known as vitamin K hydroquinone, catalyzed by vitamin K epoxide reductase (VKOR) enzyme ⁽⁹⁾. Other enzyme which is called gamma-glutamyl carboxylase or vitamin-K-dependent carboxylase then oxidizes vitamin-K hydroquinone, and permit carboxylation of Glu to Gla ⁽¹⁰⁾. The process of carboxylation takes place only if the carboxylase enzyme can simultaneously oxidize vitamin K hydroquinone to vitamin K epoxide. It is said that the carboxylation and epoxidation reactions are linked. Vitamin K epoxide is then transformed by VKOR into vitamin K. This reduction and consequent reoxidation of vitamin K,

along with the carboxylation of Glu, is named the vitamin K cycle this cycle subsist in the liver cells endoplasmic reticulum⁽¹¹⁾.

People rarely lack vitamin K1, as part of vitamin K1 is continually recycled in cells as seen in Figure 3. VKOR's activity is inhibited by warfarin and other 4-hydroxycoumarins. This decreases the levels of vitamin K hydroquinone and vitamin K in the tissues, thus rendering the glutamyl carboxylated

reaction inefficient. As a consequence, clotting factors with insufficient Gla are generated. With lack of Gla on the amino ends of these factors, they do not bind efficiently to the endothelium blood vessel and cannot stimulate coagulation to enable clot formation when tissues injury occurs. Since it is difficult to estimate the dose of warfarin to suppress coagulation, warfarin must be strictly monitored to prevent overdose⁽¹²⁾.

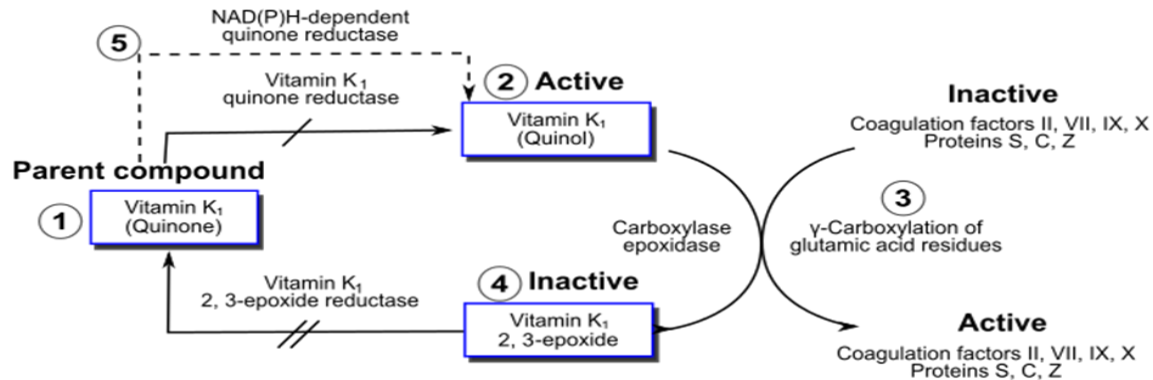


Figure 3. Vitamin K cycle⁽¹³⁾

Gamma-carboxyglutamate proteins

Gamma carboxyglutamate protein (Gla proteins) is secretory protein present in the body fluids or extracellular matrix. Gla-residues make up a powerful calcium binding group in the proteins to which they bonded, in all situation Gla-residues are essential to the functioning of these proteins⁽¹⁴⁾.

Until recent years, there have been 17 human proteins identified to be Gla domains: the blood clotting factor II (prothrombin), factor VII, factor IX and factor X, the anticoagulant protein S, protein C, and protein Z (factor X-targetting), Osteocalcin (bone Gla protein), the matrix Gla protein (MGP) which inhibit calcification, growth arrest sequence 6 protein (Gas6) which regulate cell growth, and four transmembrane Gla Proteins (TMGPs) the function of these proteins until recent years unknown. The Gas 6 protein may have growth factor function that stimulate AXI tyrosin kinase receptors and activate cell growth or avoid apoptosis programmed cell death) in some cells⁽¹⁵⁾ (Table 3).

Table 2. Types and functions of 17 Gla-proteins⁽¹⁴⁾

Name of protein	function
Prothrombin, factors VII, IX, and X	Haemostasis (pro-coagulant function)
Proteins S, C, and Z	Haemostasis (anticoagulant function)
matrix Gla protein (MGP)	Inhibit arterial calcification
Osteocalcin	Bone metabolism
Growth arrest sequence 6 protein (Gas6)	Regulation of cell growth
Periostin	Bone metabolism, cell migration, angiogenesis
Gla rich protein (GRP) Periostin like factor Four transmembrane Gla protein	Function unknown

Functions of Vitamin K

Effect of vitamin K on coagulation

Vitamin K, which is a coenzyme used to generate coagulation factors, is long considered to be important for controlling blood clotting. Blood coagulation is based on the cascading stimulation of a number of coagulation factors (specific proteins) that form blood clots which prevent bleeding. Vitamin K acts as an enzyme cofactor which catalyzes carboxylation (insertion of a carboxy group-COOH) of some glutamic acid residues to gamma-carboxyglutamate (Gla) in the coagulation factors. Vitamin K has critical significance in the

stimulation of a total of seven clotting factors⁽¹⁶⁾. Gamma-carboxylation based on vitamin K allows these clotting factors for binding to calcium ions (Ca^{2+}) and to activate the mechanism of coagulation. Clotting factors II (prothrombin), X, IX and VII form the coagulation cascade center, whereas protein Z tends to increase the function of thrombin, which is the key enzyme in blood coagulation, via raising thrombin binding to cell membranes phospholipids. Protein Z, protein S, and protein C have inhibitory function of coagulation. These proteins control (coagulation time) and manage the cascade of coagulation. Protein S is a subject of fundamental study of vitamin K-dependent proteins because of its complexity and variety of functions in the body⁽¹⁷⁾. The human body stores significantly low quantities of vitamin K and quickly exhausts its reservations if there was no periodic dietary intake. A recycle process of vitamin K (vitamin K cycle) enables a little quantity of vitamin K to actively engage many times in the gamma carboxylation of the proteins, thus reducing the requirement for vitamin K from diet. Significant deficiencies of vitamin K causes prolonged time of coagulation and rise the hazard of sever bleeding, blood loss, bruise, poor healing of wound and anemia⁽¹⁸⁾.

Effect of vitamin K on bone health

Vitamin K and vitamin D are important for the healthy metabolism of the bone. Three proteins dependent on vitamin K were isolated from the bone: S protein, matrix Gla protein (MGP) and osteocalcin, Osteocalcin is synthesized by osteoblasts (Cells forming bone) and participates in mineralization of bone, after collagen osteocalcin is the most crucial protein being integrated in the bone matrix. While vitamin D enhances osteocalcin production and increased the amount of calcium, Vitamin K activates osteocalcin via vitamin K – dependence carboxylation of 3 of its glutamic acid residues. This activated form of osteocalcin will bind and store calcium (hydroxylated calcium phosphate) in bones. Inadequate osteocalcin carboxylation (e.g. due to deficiency of vitamin K) can cause bone density loss. Matrix Gla protein are located in cartilage, bones, and soft tissue like blood vessels. Experimental studies show that MGP hinders cartilage and soft tissue hardening, while it improves normal bone growth and development^(19, 20).

Protein S (which is vitamin K – dependence anticoagulant protein) had been also synthesized via osteoblast but its function in bone metabolism is still unclear.⁽²⁰⁾ Children suffering from inherited deficiency of protein S have increased coagulation and reduced bone density complications⁽¹⁹⁾. Postmenopausal women are more susceptible to bone loss and osteoporosis due to reduction in estrogen level after menopause⁽²¹⁾. Several random trails have evaluated the impact of phylloquinone

treatment on bone loss in postmenopausal women^(22- 24). Treatment of post menopause women with a large dose of phylloquinone (1000ug/day) plus vitamin D, magnesium, calcium and zinc over a period of 3 years was shown to reduce bone loss on the femoral neck but not on the lumber spine in women between 50 and 60 years of age⁽²²⁾. Moreover, in a randomized, double blind placebo controlled trail, 5 mg daily supplement of phylloquinone in 440 postmenopausal women suffering from osteopenia for 2 years induced more than 50 percent diminish in clinical fracture in comparison with placebo⁽²³⁾. Knapen et al. Followed healthy postmenopausal women who have obtained either placebo or MK-7 capsules (180 mcg / day) for three years. In the first year, bone loss rates were comparable in both groups, but after 3 years period MK-7 affected bone health positively compared to placebo even after BMI and age adjustment⁽²⁴⁾.

Effect of vitamin K on cardiovascular diseases

Calcification of the blood vessels is an active process causing cardiovascular disease (CVD) which causes the world's largest killing. Vitamin K-dependent proteins are known to stimulate the protection mechanism to prevent the occurrence of blood vessels calcification⁽²⁵⁾. A vitamin K-dependent carboxylation activates matrix Gla protein (MGP) and can probably reduce calcium deposit on the blood vessels lining^(26, 27) and the elevated blood concentration of inactive, under-carboxylated MGP is considered as a probable indicator for (early) atherosclerosis (24). A case control study found that administrating of 500 micrograms per day of vitamin K1 for 3 years could delay the development of early calcification of coronary artery among older men and women⁽²⁹⁾. Besides from its effect on MGP, vitamin k may inhibit blood vessels calcification via anti-inflammatory mechanism. Vascular calcification is a process of chronic inflammation through which macrophages are activated causing production of proinflammatory cytokines such as TNF- α , oncostatin M, IL-6, and IL-1 β . These proinflammatory cytokines stimulate osteogenic differentiation of blood vessels smooth muscle cells. Vitamin K has anti-inflammatory effect by blocking NF-kB signal transduction, thus inhibits progression of blood vessels calcification⁽²⁸⁾. In a cross-sectional study conducted with 662 community-dwelling adults from the Multi-Ethnic Study of Atherosclerosis (MESA). High levels of blood phylloquinone are inversely correlated with many blood inflammatory markers like CRP, IL-6 and soluble intercellular adhesion molecule-1 (ICAM-1)⁽³⁰⁾.

Several clinical trials demonstrate Vitamin K as an atherosclerosis protective factor and that low concentration of phylloquinone could be correlated with an increased hazard of blood vessels

calcification^(31, 32). It is especially true when older people take antagonists of Vitamin K to reduce blood clotting⁽³³⁾.

Effect of vitamin K on nervous system

In the brain tissue, high levels of vitamin K are found and shown being essential for the function of brain. Vitamin K could help to prevent old age neurodegenerative diseases by reducing calcification (hardening) of soft tissue. Inside the brain, vitamin K is implicated in synthesizing of sphingo-lipids (a group of complex lipids in all mammalian cells where they are crucial parts of the cell membrane) which are found in the central and peripheral nervous systems cells at principally high concentrations⁽³⁴⁾. Some sphingolipids have a strong correlation with MK-4. Inside brain sphingolipids are the main players in important cellular incident like senescence, differentiation, proliferation, interaction between cells and transformation. Research in recent years has linked changes in the metabolism of sphingolipids to the process of aging and neurological diseases, like Parkinson disease and Alzheimer's disease (AD). There are also two Vitamin K – dependent proteins (VKDPs), namely Gas6 and, to a less degree, Protein S which have been strongly linked with nervous system. Gas6 is one of a secreting proteins contain 11–12 Gla (carboxyglutamic acid) residues. Gas6 were implicated in chemotaxis, cell growth, mitogenesis, and myelination in the nervous system. Protein S has initially been found to have a role in blood clotting as co-factor for protein C, although limited in range data gathered up to now indicate that protein S is able to protect the nervous system and brain through its anti- thrombotic and neuroprotective signaling mediating functions^(34,35).

Effect of vitamin K on insulin sensitivity

Vitamin K may have a beneficial impact on the balance of blood sugar and thus help prevent diabetes. The molecular mechanisms behind vitamin K's beneficial function in the responsiveness of insulin and glucose homeostasis are:

1-Osteocalcin activation (by vitamin K- dependent carboxylation) : OC can boost proliferation of B-cells, expressions and secretion of insulin as well as, enhance expression of adiponectin in the adipocytes , which indicates OC's role in the regulation of glucose metabolism through improvement in the function of B-cells and insulin sensitivity^(36, 37, 38).

2-Adipokines production regulation: alteration in the levels of circulatory adipocytes derived factors (adipokines) has a significant role in insulin resistance^(39, 40). After a year of follow up, people who raise their nutritional phylloquinone consumption showed that inflammatory cytokines such as leptin, interleukin (IL)-6, tumor necrosis factor (TNF) and other risk factors of metabolic syndrome which are related to diabetes and insulin resistance, such as visfatin and ghrelin are

significantly reduced compared with subjects who do not alter their dietary phylloquinone intake amount. Meanwhile it is reported that adiponectin, which is well known adipokines that has positive regulation for insulin sensitivity are significantly increased after dietary dose of phylloquinone (1000mg per day for 4 weeks) in premenopausal women⁽⁴¹⁾.

3-Anti-inflammatory function of vitamin k: The most commonly-researched proinflammatory cytokines that induce insulin resistance are TNF- α and IL-6^(42, 43). The study has shown an Inverse relation between the state of vitamin K and inflammatory circulatory markers. The mechanism behind vitamin K's beneficial function against production of proinflammatory cytokines is uncertain. Nevertheless, vitamin K has been shown to inhibit NF-KB leading to decline in production of IL-6 and other type's cytokines⁽⁴⁴⁾.

Effect of vitamin K on cancer

Vitamin K2 was studied as supplement of cancer treatments in many clinical interventions⁽⁴⁵⁾. In vitro experiments, supplementation of K2 was found alone to stop numerous cancer cell lines from growing and metastasizing^(46, 47). The mechanisms through which vitamin K2 inhibits cancer growth and metastasis, In brief, vitamin K2 can function in many ways, such as protein kinase C, protein kinase A, steroid, kappa B nuclear , and xenobiotic receptor⁽⁴⁸⁾. In addition, there are numerous cases in which K2 addition alongside standard therapy subside the progression of cancer, including some cases in which patients have reached full remission^(45,49). The action of vitamin K2 as an anti-cancer agent is not restricted to a definite type of cancer but has been identified in many forms of cancer⁽⁴⁸⁾.

Effect of vitamin K on kidney

The state of dephosphorylated-uncarboxylated-MGP (dp-ucMGP) is an established vitamin K deficiency research marker first recorded in chronic kidney disease (CKD) patients⁽⁵⁰⁾. dp-ucMGP is attributed to CKD progression, since later stage CKD people have high circulating concentrations of dp-ucMGP^(51, 52,53,54). Supplementation of vitamin K2 shows improved function of renal artery and help stop further progression of calcification in renal artery⁽⁵⁵⁾. Furthermore, vitamin K2 supplementation has been shown to enhance glomerular filtration in a treatment protocol. In CKD researches the importance of vitamin K2 is excellent and many comprehensive studies are under way using vitamin K addition to treat CKD patients^(56, 57).

Effect of vitamin K on immune system

Over the last few years in vivo experiments explained a previously unidentified immunomodulatory function of vitamin K2. Firstly, it has been shown that MK-7 modulated IL-1alpha,

TNF alpha, and IL-1 β expression⁽⁵⁸⁾. Besides that, K2 lowers T-cell proliferation in healthy subjects, whilst still vitamin K1 has no influence. It has been also confirmed by T-cells from numerous children suffering from atopic dermatitis and healthy children, as well as other study including patients on dialysis^(59, 60). Both studies have shown that K2 reduces the number and proliferation of activated T-cells. Accumulated evidence thus shows that K2 has a new role as an immune-suppressive agent. This requires further explanation; till now, a unique physiological mechanism can be speculated by which vitamin K2 can promote immunomodulation but needs further study^(58, 61).

Effect of vitamin K on skin health

Wound healing considered as a complex and essential physiological process which involves the cooperation between many cell strains and their products. The stages of wound healing include coagulation, epithelization, collagenation and tissue renovating. Accelerating the healing of skin injuries is a very important issue for patients and physicians. Vitamin K's topical application raises the rate of wound contraction significantly. Topical vitamin K was reported to stimulate wound healing, possibly because it can significantly increase the rate of wound contraction, enhance epithelialization duration, build up of fibroblast cells, formation of collagen fibers and blood vessels and increase in hydroxyprolin quantity in the experimental models. In addition, the blood coagulation system is reported to facilitate angiogenesis and wound healing. Since vitamin K has an impact on γ -carboxylation of some coagulation factors, its effect upon blood

coagulation systems can be the reason of the wound healing action of vitamin K. Other studies show that vitamin K is effective antioxidant and it can also improve wound healing on the basis of its antioxidant properties. Vitamin K can therefore be used in addition to other established therapies in patients with acute and chronic skin injuries as a supplemental medication^(62, 63).

Effect of vitamin K on testosterone hormone

Vitamin K (K) is essential in post translation modifying of blood - clotting factors and proteins in the bone matrix (Gla proteins). In the previous study, DNA microarrays were used and genes whose expression in the K-deficient state of the testis was affected were identified. In the vitamin K deficient group, expression of genes participating in the biosynthesis of cholesterol and steroid hormones was reduced. The mRNA levels of Cyp11a (a testosterone synthesis rate-limiting enzyme) is positively correlated by menaquinone-4 (MK-4) level in the testis. In addition, the plasma and testis of the K-deficient population had lower testosterone concentrations in comparison with the control and vitamin K-supplemented groups. These findings indicate that K is participated in the production of steroids in the testis via the Cyp11a regulation⁽⁶⁴⁾.

Deficiency of Vitamin K

The vitamin K requirement depends on age and gender. Table 2 displays the average recommended daily quantities in micrograms (mcg).

Table 3. Amount of vitamin K needed in different groups of people⁽⁶⁵⁾.

Age	Male	Female	Pregnant	Lactating
0 – 6 months	2.0 mcg	2.0 mcg		
7 – 12 months	2.5 mcg	2.5 mcg		
1 – 3 years	30 mg	30 mg		
4 – 8 years	55 mcg	55 mcg		
9 – 13 years	60 mcg	60 mcg		
14 – 18 years	75mcg	75mcg	75 mcg	75 mcg
19 – 50 years	120 mcg	90 mcg	90 mcg	90 mcg
51 – 70 years	120 mcg	90 mcg		
70 + years	120 mcg	90 mcg		

Deficiency of vitamin K is very rare. Many individuals receive adequate vitamin K from their foods. Bacteria in the colon also produce some vitamin K which can be absorbed by the body. However, some groups of people can find it difficult to get adequate vitamin K:

1- children: Osteocalcin is among the most common proteins in the body and is at least 10-times higher during growth than when the peak of bone mass has been achieved. It means that children have a much

greater vitamin K need than adults. Unfortunately, an rise in snacks and fast-food consumption has led to a decline in child vitamin K intake year after year⁽⁶⁶⁾.

2- Pregnant women. Vitamin K is a fat-soluble vitamin that ensures it is not distributed easily through the placenta. However, the growing fetus requires vitamin, which is derived from the bloodstream of the mother. The vitamin K level of mother was shown to decline in particular during the

third trimester of pregnancy and the addition of vitamin K improved carboxylation of osteocalcin in both mothers and the offspring (cord blood measurement) ⁽⁶⁷⁾.

3- Early infancy. There is a short window from conception to 6 months if the human baby is exposed to a minimal but life-threatening hazard of bleeding. Late onset vitamin K bleeding (occur at ages between 3-8 weeks) usually leads to death or permanent neurological damage in infants due to intracranial bleeding, the main nutritional danger for infants who've been breastfeeding predominantly ⁽⁶⁸⁾

4- Elderly. Osteocalcin carboxylation (as an indicator for generic vitamin K state) has been reported to decrease after 50 years. It can be associated with a decreased intake of food, poorer intestinal absorption or increased demand. It correlates significantly with the beginning of age-related symptoms such as calcification of blood vessels and increased bone loss. Such processes are, of course, multi factorial, but risk factors accumulation typically increases the risk ⁽⁶⁹⁾.

5- People with intestinal absorption impairment. Crohn's disease, cystic fibrosis, and galactosemia are all reportedly chronic diseases linked to poor vitamin K status ⁽⁷⁰⁾.

6- Some medicines that can interfere with vitamin K. such examples are as follows:

- Warfarin (Coumadin ®): Vitamin K interacts seriously with warfarin (blood- thinner drug). If warfarin is taken it must ensure that the same amount of vitamin K taken from diet and supplements every day. abrupt alteration in vitamin K consumption may result in harmful bleeding (when less consumed) or blood clots (if more consumed) ⁽⁷¹⁾.

- Antibiotics may kill good intestinal bacteria. Many of these bacteria produce vitamin K. Consuming antibiotics for even more than a few weeks may decrease the quantity of vitamin K produced in the intestines and thus the amount accessible for the body to be using ⁽⁷²⁾.

- Bile acid sequestrants drugs (like cholestyramine [Questran ®] and colestipol [Colestid ®] which are used by certain people to reduce cholesterol level in blood. These medicines can reduce body's absorption of vitamin K particularly if were taken for many years ⁽⁷³⁾.

- Orlistat (Alli ® and Xenical ®) is a therapeutic drug that loses weight. This decreased fat absorption in the body and can lowered vitamin K absorption ⁽⁷⁴⁾.

Vitamin K Importance in Infants

Transportation of vitamin K over the placenta is low and the hazard of vitamin K deficit in the newborn babies is increased. Deficiency in vitamin K may lead to vitamin K deficiency bleeding (VKDB), a disorder previously known as "classic hemorrhagic disease of newborn," within the first few weeks of life. VKDB is linked to

umbilical, gastrointestinal, nose, skin, and other sites bleeding. VKDB is described in the first week of existence as a "early VKDB" While " Late VKDB" exists at 2-12 weeks of age, particularly in breastfed infant children because of the low level of vitamin K in breast milk or malabsorption trouble in infants (such as cystic fibrosis or cholestatic jaundice) ⁽⁷⁵⁾.

VKDB, especially late VKDB, may also appear as abrupt cranial bleeding which has a high death risk. The American Academy of Pediatrics recommends a single dose of vitamin K1(0.5 -1 milligram (mg)) given intramuscularly at birth, in order to avoid VKDB ⁽⁷⁶⁾.

Safety and Toxicity of Vitamin K

While allergic reactions may be likely, no well-known toxicity linked to high doses of vitamin K1 (phylloquinone) or vitamin K2 (menaquinone). The same would be not correct for synthetic vitamin K3 (menadione) as well as its derivatives. Menadione can inhibit the function of glutathione, a natural antioxidant in the body, which contributes to oxidative stress related cell membranes damage. Menadione administered by injection caused jaundice, hepatotoxicity, and hemolytic anemia (because of erythrocytes rupture) in babies; thus menadione is not used for deficiency of vitamin K anymore ⁽⁷⁷⁾. In addition, high doses of vitamin A and vitamin E were establishing to antagonize vitamin K. large dose of vitamin A effect the absorption of vitamin K while vitamin E can suppress vitamin K activity in γ -carboxylation of glutamate residues and influence the cascade of coagulation ⁽⁷⁸⁾. People who have taken anti-coagulatory drugs such as warfarin and those with a deficiency in vitamin K are not allowed to take vitamin E supplements without near medical attention due to increased risk of excess bleeding (haemorrhage) ^(79:1).

Conclusion

Vitamin K is an essential fat soluble vitamin which is important for blood clotting. It serves as a coenzyme which facilitating the gamma carboxylation of calcium binding proteins' glutamic residues. Beside its effect on coagulation vitamin K has a number of possible impacts on human health and that low levels of vitamin K are related to different aspects of human diseases. Several clinical studies hypothesized that a vitamin K rich diet and / or vitamin K treatment might have numerous health benefits which includes, preventing bone mass loss, delay the development of blood vessels calcification, prevent old age degenerative diseases, improve blood sugar balance, stop numerous cancer lines from growing and metastasizing, enhance function of renal artery, accelerate healing of skin injuries, modulate immune function as well as increase production of steroids in the testis. Larger trails should be made to better clarify the detrimental

long-term impact of vitamin K deficiency, and whether these can be avoided by additional vitamin K institution.

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