VITAMIN K-SOURCES, PHYSIOLOGICAL ROLE, KINETICS, DEFICIENCY, THERAPEUTIC USE AND TOXICITY

Neama Mahmoud Taha*

Department of Public Health, Health Sciences College at Al-Leith, Umm Al-Qura University

Abstract

As vitamin K is required for the post-transnacional alteration of seven proteins involved in this cascade, it has historically ben associated with blood coagulation. But it also helps additional 11 or 12 proteins that have distinct functions mature. These roles include controlling the calcification of connective tissues. Numerous studies have been conducted to determine whether vitamin K may be linked to the prevention of osteoporosis and cardiovascular problems because this process is pathological in arteries but physiologically necessary in bones. We regretfully cannot draw firm conclusions about such a link at this time given the state of our understanding.

The variety of vitamin K's biological activity-which is not limited to a single component but rather encompasses both synthetic congeners (K3 and K4) and natural forms of vitamin K found in plants and animals (K1 and K2). Vitamin K1, also known as phytoquinone, is present in several veggies. Menaquinones, or vitamin K2, are a class of chemicals (MK4–MK13) mostly derived from bacteria and are primarily found in fermented cheeses.

Aim: Vitamin K plays a multifaceted role in our bodies, extending beyond its well-known function in blood coagulation

Keywords: Vitamin K-sources, physiology, kinetics, deficiency, therapy, toxicity

Manuscrito recibido: 10/02/2024
Manuscrito aceptado: 24/02/2024

*Corresponding Author: Neama Mahmoud Taha, Department of Public Health, Health Sciences College at Al-Leith, Umm Al-Qura University

Correo-e: Neama_mt@yahoo.com

Introduction

Many physiological and biological processes depend on vitamins, and deficiencies in these nutrients have a number of negative effects on human health. In contrast to deficiencies in vitamins A, B, C, D, and E, vitamin K (VK) deficiency is not frequently treated, despite its natural dietary sources and potential health effects on human physiology, including blood coagulation. Although much of the behavior is still understood, the VK family is significant for a number of biological functions and is classified into a number of unique subtypes based on the length of side chains made up of isoprenoid families (Rajagopal et al., 2022).

The importance of vitamin K in blood coagulation is widely acknowledged. It was thus given the name "vitamin K," which is derived from the German word for coagulation. The 1943 Nobel Prize in Physiology or Medicine was awarded to Henrik Carl Peter Dam and Edward Adelbert Doisy for their discoveries of vitamin K and its chemical makeup, respectively, and the Nobel Committee for Physiology or Medicine recognized the importance of this discovery (Mladěnka et al., 2021).

A class of similar compounds that have the same physiological function as this vitamin is referred to as having vitamin K (Fig. S1 in the online Supporting Information). The core of menadione, or 2-methyl-1,4-naphthoquinone, is shared by both compounds. The most basic form, known as vitamin K3, is composed solely of this core. Unlike its native forms, K3 is hydrophilic and not obtained by food. Nonetheless, it plays a role in human metabolism as a mediator. Vitamin K can be found in plants (phylloquinone, also called phytomenadione or phytonadione) or, more commonly, in animals (as vitamin K2). Additionally, there is vitamin K4, a term that is associated with additional synthetic versions of vitamin K. It might be one of the ester forms of vitamin K3, such as vitamin K3 diacetate, or menadiol, the reduced form of the vitamin (Mladěnka et al., 2021).

The primary form of vitamin K in the human diet is vitamin K1 (phylloquinone). Green leafy vegetables contain it as a nutrient that is ingested. You can get vitamin K2 (menaquinone, or MK) from bacteria in the large intestine and from eating meat, dairy products, and fermented meals. Menaquinone-7 (MK-7) is a kind of vitamin K2 that can be found in dairy products, some fermented or cultured vegetables, and dietary supplements. Japan has been consuming natto, a fermented soybean snack, for generations and it is one of the main dietary sources of MK-7. Much of the current progress in using MK-7 as a vitamin K source comes from research showing its improved bioavailability over vitamin K1 and other menaquinone homologs (Marles et al., 2017).

Literature review

A class of structurally related substances that are vital to animal and human nutrition is known as vitamin K. Vitamin K1 is phylloquinone, which is commonly found in leafy green vegetables, while vitamin K2 is found in fermented foods. Although synthetic vitamin K counterparts such as menadione and its derivatives are prohibited for human consumption, they are nevertheless utilized in animal feeding. Although its function in blood coagulation is the most well-known, vitamin K also plays a part in bone health, inflammatory regulation, and the avoidance of artery hardening. Phylloquinone is a component of Photosystem I and takes part in photosynthetic electron transport (Tarento et al., 2019).

Vitamin K-sources

Green plants, algae, and cyanobacteria are examples of photosynthetic organisms that contain a single molecule called vitamin K1. Phylloquinone was formerly believed to be exclusively found in chloroplasts because of the high vitamin K1 level in green portions of plants, but additional study has shown that it is also present in peroxisomes and plasma membranes. Some non-photosynthetic parasitic plants also have it. Broccoli, brussels sprouts, cabbage, and other green cruciferous vegetables are excellent providers of vitamin K1, but phylloquinone level is also high in spinach, chard, parsley, and different kinds of lettuce. All of the plant's edible green sections are generally regarded as a significant source of vitamin K1. Naturally, this also holds true for edible wild plants (Tarento et al., 2019).

Since vitamin K1 is the most common type of vitamin K found in food supplements and medications recommended for vitamin K insufficiency, a significant amount must be produced. The process of condensing naphthoquinone with isoprenoid precursors yields synthetic vitamin K1. Research is being conducted to find effective production methodologies in response to the growing demand for vitamins derived from natural sources and produced sustainably. Utilizing microalgae and cyanobacteria, which can be cultivated in bioreactors under extremely controlled circumstances and produce a sizable amount of vitamin K1, is one viable approach. This remains valid even in cases when traditional aquaculture methods are employed to cultivate the algae (Tarento et al., 2018).

Dairy products are one of the main sources of vitamin K2 in the human diet. Because of the bacterial fermentation that takes place during production, cheeses are very rich sources. In actuality, cheese provides roughly half of the vitamin K2 that humans consume (Mladěnka et al., 2021).

Vitamin K chemical structures and nomenclature

All lipid-soluble compounds that have cofactor activity for the carboxylase enzyme, which converts glutamate residues to γ-carboxyglutamate (Gla) residues, are collectively referred to as vitamin K. These compounds share the same structure, known as menadione, which is a 3-methyl-1,4-naphthoquinone. This compound's side chain is composed of several isoprenoid units at the 2-position. Because of study into the origin of bleeding tendencies in hens that were given a diet that was lacking in both fat and what is now known as vitamin K, the letter K is derived from the German term coagulation. This is because vitamin K is now recognized as the coagulation vitamin.In addition to the five naturally occurring forms of vitamin K, there is also phylloquinone, which is referred to as "phytonadione" by the United States Adopted Names Council and is classified as vitamin K1 in the United States Pharmacopeia, as well as the MK series, which are collectively referred to as vitamin K2. (Marles et al., 2017) (Figure 1).

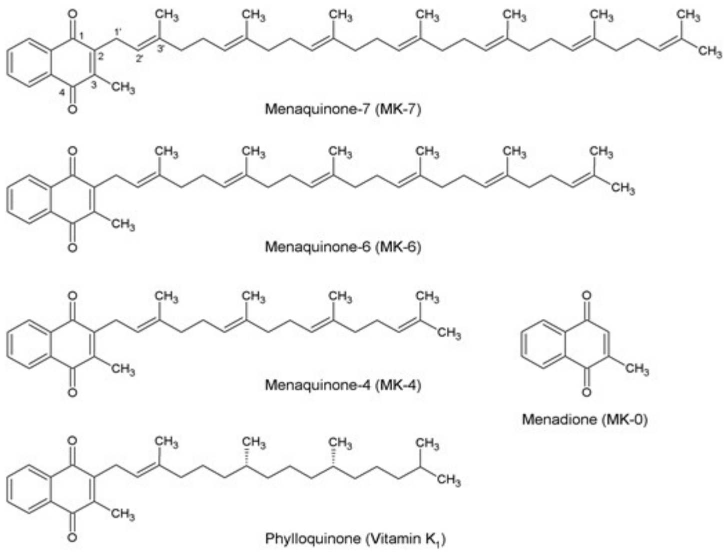

Figure 1. Vitamin K chemical structures and nomenclature (Marles et al., 2017).

Vitamin K - physiological role

The process of blood coagulation is one of the physiological processes that need the presence of vitamin K as a cofactor. This is because vitamin K-dependent proteins are responsible for converting peptide-bound glutamate to γ-carboxyglutamate. The γ-carboxyglutamyl carboxylase, vitamin K epoxide reductase, and ferroptosis suppressor protein-1—the latter of which was recently discovered as the long-sought-after warfarin-resistant vitamin K reductase-all contribute in the vitamin K cycle, which propels this process. Vitamin K also performs actions that are independent of carboxylation. Similar to ubiquinone, vitamin K inhibits ferroptosis, a form of cell death characterized by lipid peroxidation, and serves as an electron transporter for the synthesis of ATP in certain organisms. In this Perspective, we give a summary of the several roles that vitamin K plays in physiology and metabolism while also discussing its potential involvement in ferroptosis in conjunction with ferroptosis suppressor protein-1. From an evolutionary standpoint, a comparison between vitamin K and ubiquinone could provide additional understanding of the various functions of vitamin K in biology (Mishima et al., 2023)

Vitamin K-kinetics

Absorption

It is clear that different forms of vitamin K have varying absorption rates. In general, bile salts help produce mixed micelles, which allow enterocytes to absorb naturally lipophilic forms of vitamin K. Once the vitamin has been further packaged into chylomicrons inside entero-cytes, it enters the lymphatic system and proceeds throughout the body. The co-presence of fat, as in dairy products, facilitates good and possibly total absorption of vitamin K2, especially long-chain MKs. In contrast, vitamin K1 is less easily absorbed from the diet than dietary MK-7 or pure MK-4. Pure vitamin K1 has a lower bioavailability than pure MK-7, but a higher bioavailability than pure MK-4, pure MK-9, or dietary vitamin K1. As previously indicated, dietary vitamin K1 is firmly attached to plant tissue, which makes pure vitamin K1 more readily absorbed than the food version. Researchers find that cooking does not increase the absorption of vitamin K1, nor does it change the bioavailability of the nutrient in different vegetables. However, fat enhances the bioavailability of vitamin K1 from plant sources by approximately three times, although it is still significantly lower than that of vitamin K1 that has been commercially solubilized (Mladěnka et al., 2021).

Distribution And Elimination

Experiments show that the distribution of vitamins K1 and MK-4 is different. Vitamin K1 levels in the liver were much higher in rats given the same oral dosage than MK-4, but the opposite was seen in the aorta. Examinations of post-mortem human livers, where vitamin K1 was routinely detected in higher concentrations than MK-4, provided more evidence in favor of this. It is noteworthy that the levels of MK-7 to MK-11 in human blood were substantially higher than the levels of vitamin K1. One study indicated that liver samples from people without cancer and those with cirrhosis or hepatitis did not differ in their levels of vitamin K1 or MK-7 to MK-9; however, there was a noticeable difference in the levels of MK-10 to MK-13. It was discovered in that investigation that MK-10 and MK-11 were primarily located in the mitochondria (Mladěnka et al., 2021).

Vitamin K Deficiency

One often-ignored illness that has a substantial influence on health across multiple physiological domains is vitamin K insufficiency. Vitamin K is a class of fat-soluble chemicals that plays a vital role in bone metabolism, blood clotting, and cardiovascular health. A lack of vitamin K in the human body can lead to a variety of issues, such as hemorrhage, poor bone growth, and increased cardiovascular risks. Healthcare practitioners must comprehend the complex interactions between vitamin K and these essential physiological processes (Eden, 2023).

Haemorrhage, or bleeding, is the primary sign of a vitamin K deficiency. This can occur in the stomach, gut, nose, wound, or skin, resulting in bruises. Vomiting blood can occasionally result from gastrointestinal hemorrhage. Stools may be tarry dark or there may be visible blood in the urine. Life-threatening hemorrhage inside or around the brain can happen to neonates. Because the liver produces clotting factors, having a liver disease raises the risk of bleeding. Insufficient vitamin K can also erode bones (Johnson, 2024).

Therapeutic use

Vitamin K deficiency in adults: In order to treat vitamin K deficiency in adults, the National Academy of Science Food and Nutrition Board recommends that men and women consume at least 120 μg and 90 μg of vitamin K daily, respectively, by food and/or oral supplementation. For vitamin K1 deficiency, a maximum oral dose of 25 mg is advised, with a recommended range of 1 to 2 mg. Vitamin K1 dosages for anticoagulant-using patients usually range from 1 to 10 mg. Generally speaking, the maximum impact of oral medication is seen 24 hours following the intake (Eden, 2023).

Prophylaxis in newborns: Usually, intramuscular injections of 0.5 to 1 mg of vitamin K1 are given during the first hour of life as prophylaxis. As an alternative, babies can get an oral dose of 2 mg of vitamin K1 at birth, with subsequent doses between days 4 and 6, as well as between weeks 4 and 6. An alternative method involves giving newborns 2 mg of vitamin K1, which is then followed by weekly dosages of 1 mg for three months. It is noted, nonetheless, that because intramuscular injection has a higher efficacy, it is preferable in neonates (Eden, 2023).

Vitamin K- toxicity

Very few incidences of natural vitamin K systemic toxicity in people or animals have been documented. There have been worries that excessive coagulation may occur from consuming large amounts of vitamin K. Nevertheless, this remains unobserved, potentially because of the restricted locations for γ-carboxylation. Quite the reverse, as rare human case reports have shown, can result in hypoprothrombinemia from extremely high vitamin K dosages. Excessive dosages in animals have caused anemia and bleeding.

Based on existing human data, taking 10 mg/day of vitamin K1 for a month does not result in any harmful side effects. This is in line with findings from research on animals, where using even 2 g/kg for the same length of time was safe. Generally speaking, the recorded side effects of vitamin K have only been localized, such as mild gastrointestinal problems and skin rashes that disappear after quitting treatment after receiving vitamin K2 (Marles et al., 2017).

Clinically, intramuscular vitamin K1 distribution is not particularly comfortable owing to injection site pain and skin bruising. Therefore, more advanced approaches like microneedles are being researched. It should be highlighted, therefore, that excessive dosages of vitamin K3 have the potential to produce a toxic response that includes hemolytic anemia in a dose-dependent way, especially in babies. Redox-cycling, which is most likely connected to this process, is impeded in natural vitamins K1 and K2 by the presence of unsubstituted position 3, which is extremely reactive and binds thiol groups to create thioethers (Simes et al., 2020).

Conclusion

Coagulation has always been associated with vitamin K. While there is a valid relationship here, vitamin K plays a variety of other roles in human physiology. Of the eighteen or nineteen proteins that require vitamin K for posttranslational modification, eleven or twelve have nothing to do with coagulation. Specifically, its role in calcification of connective tissue has sparked a great deal of investigation, however the results are still unclear. A single vitamin K molecule does not exist. Indeed, the diversity and disparate biological properties of the many forms of vitamin K might explain why research done so far has not been able to conclusively identify the role of vitamin K in humans. It appears that more research, especially prospective clinical studies, are required to elucidate its non-coagulation-related effects in people. Nevertheless, natural vitamin K supplements are generally safe and, for that reason, appropriate in certain situations, such postmenopausal osteoporosis.

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