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Role of Vitamin K2 in Human Body: A Mini Review

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Abstract

Vitamin K2 (Menaquinone) stands out from other members of the vitamin K family due to its unique molecular structure. It is primarily found in meat and dairy products or converted from K1 in the gut. The conversion process of K1 to K2 in animal tissues, along with the role of intestinal bacteria in K2 production, is crucial for maintaining adequate levels. Extensive research has highlighted the importance of vitamin K2 in promoting bone health, preventing arterial calcification, and enhancing cardiovascular health. Additionally, vitamin K2 supports fertility and growth, and is associated with reducing the risk of cardiovascular diseases and certain cancers.

Keywords Vitamin K2, bone, osteocalcin, calcification

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List of abbreviations: MGP = Mmatrix Gla-protein, MK-4 = Menaquinone-4, MK-7 = Menaquinone-7

Introduction

Vitamin K is not a single compound, although it is traditionally connected with blood coagulation, but it is important in translation of 18-19 proteins [1]. The most known one is K1 also known as phylloquinone, that is mainly found in Green cruciferous vegetables (e.g., broccoli, brussels sprouts, cabbage, and kale), which are rich sources of vitamin K1 [2-4]. Vitamin K1 is essential to the blood clotting cascade by serving as a cofactor for the γ-carboxylation of vitamin K-dependent coagulation factors (including factors II, VII, IX and X) generated in the liver [5]. Vitamin K3, also known as menadione; is a synthetic form of vitamin K and is not typically found in the diet. It serves as an intermediate in the metabolism of vitamin K1 and K2. While it is not used directly by the body, it is important in the synthesis of vitamin K-dependent proteins. However, excessive intake of synthetic vitamin K3 can be toxic and is not recommended for dietary supplementation [1]. Another synthetic form is vitamin K4 (Acetomenaphthone), which plays an important role in the normal blood coagulation system. Vitamin K4 arrests the cells in S phase and induces apoptosis. Vitamin K4 can be used for the research of cancer, such as prostate cancer and osteosarcoma [6,7].

The main topic of this review is vitamin K2 (menaquinone), which is a type of fat-soluble vitamin that has been more recently understood and is distinct from vitamin K1 [8]. It is characterized by a unique molecular structure that consists of a series of 3 carbon-carbon bonds; these bonds can exist in either a cis or trans configuration, resulting in various forms of the molecule. The number at the end of the designation signifies the length of the side chain, with menaquinone-7 (MK-7) being

the form that is most closely associated with optimal health. MK-7 has been extensively researched for its numerous physiological functions. More recently, a different form of vitamin K2, known as MK-4, has been found in meat and dairy products. Unlike MK-7, MK-4 is not primarily produced by bacteria in the human gut but is rather converted from vitamin K1. Interestingly, studies have shown that MK-4 has opposite effects to those caused by a deficiency in vitamin K2. Therefore, it is crucial to differentiate between vitamin K1 and K2, as they seem to have distinct impacts on tissues outside of the liver [9-11].

Sources of vitamin K2

Typically, vitamin K is acquired from leafy greens and other vegetables, known as K1 sources. However, the MK-4 form of vitamin K2 is limited to a few foods such as butter, liver, and Natto, a fermented soy product popular in Japan. The primary way that human bodies obtain K2 is through the conversion of K1 to K2 by bacteria, which takes place in the large intestine. Interestingly, some of the produced K2 may be reabsorbed by the large intestine, helping to maintain sufficient levels of the vitamin in our body and reducing the need for regular consumption from food sources [12,13].

The level of absorption of vitamin K2 (menatetrenone-7) varied depending on the dosage, with the proportional level of absorption increasing from 9 to 21%. The tertiary forms of vitamin K2 are more easily absorbed than the primary and secondary forms, as well as phytonadione. To compare the relative bioavailability, menatetrenone-7 and menatetrenone-4 were studied in relation to each other, using a preparation of long chain triglyceride (LCT) and medium chain triglyceride (MCT). The results indicated that menatetrenone-4 had a higher relative bioavailability than menatetrenone-7, and that it had an equal bioavailability to menatetrenone-7 when combined with the LCT and MCT preparation. This suggests that the length of the isoprenoid side chain does not appear to affect the bioavailability of menatetrenone. Compared to vitamin K1, the bioavailability of vitamin K2 is lower and this difference varies within the different forms of vitamin K2. As mentioned earlier, vitamin K2 has a longer half- life compared to vitamin K1. As a result, all forms of vitamin K2 seem to be more efficient than vitamin K1 in boosting the levels of vitamin K-dependent proteins in the bloodstream [14].

Conversion of vitamin K1 to vitamin K2

There is compelling evidence suggesting that vitamin K1 can undergo a conversion to vitamin K2 within animal tissues. Initially, it was observed that menadione, a synthetic form of vitamin K, transformed into MK-4 in rats. When labeled menadione (vitamin K3) was given to both rats and hamsters, a labeled form of MK-4 was discovered in their tissues, specifically in the brain and testes. Similarly, when labeled K1 was administered to the rats, labeled MK-4 was detected in their tissues. In both instances, over 96% of the labeled K1 and menadione was retrieved as labeled K1 (in the case of consuming menadione in olive oil). MK-4 and menadione were found to be the primary labeled compounds present in the tissues [15].

This evidence suggests that the conversion of K1 to K2 is a process that occurs specifically in certain tissues, implying that different tissues have the ability to synthesize their own vitamin K requirements. Such a phenomenon is entirely plausible due to the distinct roles of vitamin K-dependent proteins in various tissues. The conversion of K1 to K2 was observed exclusively in saponification-released tissues, and administration of Warfarin depleted these tissues of both vitamin K and vitamin K-dependent proteins. The conversion of K1 to K2 seems to occur through the intermediate compound known as menadione. When animals are given K1, they excrete significant amounts of menadione and two other intermediate compounds in their urine. Additionally, menadione is converted into the other two compounds within several tissues. In

cases where labeled K1 and menadione are administered, the labeled menadione eventually replaces the labeled K1 in various tissues. The enzyme that catalyzes the conversion of menadione to MK-4 is a reductase and depends on nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), making this reaction similar to the conversion of vitamin K epoxide to vitamin K by the Vitamin K epoxide reductase (VKOR) enzyme [16].

Functions of vitamin K1

Vitamin K1 is a critical nutrient involved in blood coagulation, bone health, and cardiovascular function. It is considered essential for synthesizing clotting factors (II, VII, IX, and X) in the liver, which are necessary to prevent excessive bleeding. It acts as a coenzyme for carboxylating glutamic acid residues on these proteins, allowing them to bind calcium and function effectively [17,18]. It helps maintain bone strength by activating osteocalcin, a protein responsible for binding calcium to the bone matrix, which reduces the risk of fractures [17,19]. Vitamin K1 prevents calcification in blood vessels by activating matrix Gla-protein (MGP), contributing to arterial health and reducing the risk of heart disease [20,21]. Also, it supports cell growth and apoptosis, processes that may play a role in reducing the risk of certain cancers [19].

Role of intestinal bacteria in vitamin K2 production

Intestinal microflora in humans is well studied for its synthetic activities on vitamins. Vitamin K is produced by bacteria in the large intestine, and makes a significant, measurable contribution to known vitamin K stores in humans. Major bacteria involved are the Bacteroides and the *Eubacteria*, as well as several species of *Firmicutes* and the two common species of *Escherichia coli* and the ubiquitous and generally harmless menaquinone utilizing species, the *Veillonella*. The two *Escherichia coli* species may also convert K1 to K2, but there is no evidence that this contributes to human vitamin K status. It is likely that *Lactococci* and *Enterococci*, also which produce K2, may contribute to the overall vitamin K status of persons who have a colon, but no direct evidence of this exists. Conditions of the small intestine where absorption occurs appear to have little effect on vitamin K stores in the body, because even those with massive resection of the small intestine have normal vitamin K status. This implies that the bacterial synthesis of K2, which normally occurs further down in the colon and distal small intestine, is the most significant factor in vitamin K status [22-25].

Functions of vitamin K2

Vitamin K2 plays a vital role in the functioning of various proteins that rely on calcium. One such protein, known as osteocalcin, heavily depends on vitamin K in order to transform glutamate into gamma-carboxyglutamate. When calcium binds to the gamma-carboxyglutamate version of osteocalcin, it is stored within the bones. However, if osteocalcin is not properly transformed through carboxylation, it remains in an undercarboxylated state. In this state, osteocalcin is excreted from the osteoblasts and does not contribute to bone health [26].

Vitamin K2 is essential for activating a protein called matrix MGP, which binds calcium and helps in the construction and maintenance of strong bones, as well as preventing the hardening of arteries. MGP proteins, such as osteocalcin, are dependent on vitamin K and play a crucial role in regulating bone metabolism. Osteocalcin is produced by osteoblasts and is believed to be significant in the process of bone mineralization. Research conducted since osteocalcin's discovery in 1987 has focused on the connection between vitamin K levels and osteoporosis [27-29].

Vitamin K2 helps prevent calcium deposition in the arteries. There is evidence suggesting a connection between vitamin K-dependent proteins and heart disease, which has

prompted a clinical trial at the R&D Cardiovascular Medicine in Maastricht to investigate if vitamin K2 can hinder artery calcification. Patients with cardiovascular disease and atherosclerosis have been found to exhibit high levels of undercarboxylated MGP. Additionally, studies have indicated that a high intake of menaquinones is associated with a reduced risk of coronary heart disease. Furthermore, several animal studies have demonstrated the ability of vitamin K2 to impede the progression of existing arterial plaques, in addition to its preventive effects against cardiovascular disease [30-32].

A study found that a higher dietary intake of vitamin K2 is associated with improved bone density and decreased risk of hip fractures in postmenopausal women. This study highlights the importance of vitamin K2 in maintaining and enhancing bone health, as a deficiency in this vitamin increases the risk of osteoporosis and fractures. Inadequate carboxylation of MGP is linked to various cardiovascular diseases, as it fails to perform its function, resulting in calcium deposition in the blood vessels [33,34].

Vitamin K2 is also believed to play a significant role in fertility and growth. Research suggests a connection between vitamin K2 and testosterone production in the testes, as the vitamin is found in high concentrations there. It is proposed that the vitamin K2 dependent protein Gas6 is essential for the survival of mature sperm. Insufficient intake of vitamin K2 leads to inadequate production of Gas6, which in turn causes reduced fertility. Vitamin K2 has also been linked to cancer prevention and is considered an essential nutrient for energy production and overall good health [35].

Deficiency and supplementation

The Food and Nutrition Board has not yet established the recommended intake for vitamin K2. However, the Research on Osteoporosis/Periodontal Disease (ROPAD) study discovered that postmenopausal women who took a minimum of 45 micrograms of vitamin K2 daily for three years had a lower risk of vertebral fracture compared to those who received a placebo. Similarly, a controlled trial involving 325 healthy postmenopausal women found that taking 180 micrograms of vitamin K2 daily for three years led to a significant improvement in vertebral bone mineral density and a reduction in age-related decline in bone strength. Based on these findings, it is believed that consuming at least this level of vitamin K2 is necessary for maintaining optimal bone health [36,37].

Osteoporosis and an increased likelihood of cardiovascular disease are the primary indications of a deficiency in this nutrient. Numerous studies have observed a correlation between a substantial intake of vitamin K2 and a diminished chance of suffering from osteoporosis and fractures. A notable example is the "Women's Health Initiative" study, which encompassed a total of 72,327 women aged between 55 and 63. By assessing dietary intake of vitamin K1 and K2 through food frequency questionnaires, researchers discovered that consuming higher levels of both vitamins was linked to a decreased risk of experiencing a hip fracture [38,39].

A lack of vitamin K2 is a frequently encountered issue globally. The main causes of this deficiency are insufficient intake through the diet, particularly in certain regions, and the liver's inability to effectively convert K1 into K2 due to damage. When vitamin K2 levels are inadequate, uncarboxylated and inactive MGP accumulates in the arteries, leading to calcification [40]. Extensive research conducted in the Rotterdam Study, which involved 4,800 individuals aged fifty-five and above, has demonstrated a clear connection between consuming a high amount of vitamin K2 in the diet and reduced arterial calcification, as well as a lower risk of cardiovascular disease and mortality associated with it [20].

Vitamin K2 supplements have gained attention for their unique benefits, particularly in bone and cardiovascular health. Synergy with vitamin D and calcium as vitamin K2 works

synergistically with vitamin D and calcium. It helps direct calcium to the bones and teeth while preventing its deposition in soft tissues, such as arteries, where it can cause harm [(41)].

The recommended doses vary depending on age, health condition, and specific needs. Common daily doses range from 45 mcg to 200 mcg of MK-7. Vitamin K2 is generally considered safe with minimal side effects. However, individuals on anticoagulant medications (e.g., warfarin) should consult a healthcare provider, as K2 can interfere with these drugs [(42)].

As a conclusion, vitamin K2 is incredibly important for human body. It helps ensure that calcium is used properly, strengthening bones and preventing it from clogging our arteries. This means it not only supports bone health but also plays a big role in keeping our hearts healthy. Plus, Vitamin K2 is linked to better fertility and might even help in preventing some cancers. It's an essential nutrient that contributes to overall well-being in multiple ways.

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