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Vitamin K1 and K2: Biochemistry, Clinical Significance, and Therapeutic Potential in Human Health

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Abstract

Purpose of the research: This review aims to summarize current knowledge on the biological roles, absorption mechanisms, clinical relevance, and therapeutic implications of vitamin K1 and K2, with emphasis on their functions beyond coagulation.

Materials and methods: This review is based on an extensive analysis of current scientific literature. Peer-reviewed articles, clinical trials, meta-analyses, and cohort studies were identified through searches conducted in databases such as PubMed, Scopus, Web of Science, and Google Scholar. Keywords included „vitamin K1", „vitamin K2", „menaquinone", „coagulation", „osteocalcin", „bone helath", „vascular calcification", „neurological functions", „neuroprotection", „supplementation", „chronic disease", „matrix Gla protein". The selection prioritized the most up-to-date and relevant publications to provide a comprehensive overview of the biochemical, physiological, and clinical aspects of vitamin K.

Results: Vitamin K1 and K2 participate in a variety of essential physiological processes, including γ-carboxylation of vitamin K-dependent proteins involved in coagulation, bone health, and vascular integrity. Evidence supports their role in reducing the risk of fractures, vascular calcification, and cognitive decline. Additionally, vitamin K status influences outcomes in patients with inflammatory, cardiovascular, and neurodegenerative diseases. Differences in absorption and tissue distribution suggest distinct but complementary health effects of K1 and K2. Drug interactions and population-specific considerations (e.g., in newborns, pregnant women, and the elderly) further highlight the clinical relevance of vitamin K.

Conclusion: Vitamin K1 and K2 play crucial roles in maintaining systemic health beyond hemostasis. Optimizing vitamin K intake and understanding its biological complexity offer promising opportunities for disease prevention and health promotion. Further research is needed to establish standardized assessment methods and evidence-based supplementation strategies.

Keywords: Vitamin K1, Vitamin K2, Menaquinone, Coagulation, Osteocalcin, Bone Helath, Vascular Calcification, Neurological Functions, Neuroprotection, Supplementation, Chronic Disease, matrix Gla protein.

Introduction

Vitamin K (VK) is a liposoluble vitamin first discovered in 1929 by Henrik Carl Peter Dam, who observed its essential role in preventing hemorrhages in chicks fed a fat-deficient diet. Its name derives from the German word Koagulation, reflecting its central function in the coagulation cascade. The significance of this discovery was recognized by the Nobel Committee, which awarded the 1943 Nobel Prize in Physiology or Medicine to Dam and Edward Adelbert Doisy for identifying vitamin K and elucidating its chemical structure [1].

Vitamin K plays a central hepatic role in enabling the synthesis of biologically active forms of several coagulation factors, including II, VII, IX, and X, as well as natural anticoagulants such as protein C and protein S. While this classical function has long been recognized, emerging evidence points to a broader physiological relevance of vitamin K in multiple organ systems and disease processes.

This review aims to provide a comprehensive synthesis of current knowledge on vitamin K1 and K2, highlighting their biochemical properties, absorption and metabolism, clinical relevance, and potential applications in the prevention and management of chronic diseases. Special attention is given to their interactions with medications, relevance in specific populations, and implications for cardiovascular, skeletal, and neurological health.

Vitamin K1 and K2

Vitamin K exists in two main forms that share a common methylated naphthoquinone ring structure (menadione), but differ in the aliphatic side chain located at the 3′ position.

Phylloquinone (K1) is the primary form present in the human diet and is synthesized by plants, particularly green leafy vegetables such as kale, spinach, and broccoli, as well as some fruits and herbs. Additionally, certain vegetable oils, including soybean and canola oil, are rich sources of K1.

Menaquinones (K2) encompass several subtypes, distinguished by the length of their side chains, which can range from 1 to 13 unsaturated isoprene units. The number of these units is indicated by the "n" in the designation MK-n. K2 is produced endogenously by intestinal bacteria and is less widely distributed in the diet compared to K1. It is found in certain foods such as cheese, eggs, meat, and natto—a traditional Japanese fermented soybean product, which is the richest known dietary source with a concentration of 775 mcg/100 g.
K1 can be converted into menaquinone-4 (MK4) and subsequently stored in extrahepatic tissues. This conversion has been observed following oral or enteral administration, but does not occur with parenteral or intracerebroventricular routes of administration.[2]

Assessment of Vitamin K Status

Assessing vitamin K status remains challenging. Although it can be measured in plasma, the results may be influenced by abnormal lipid profiles. Moreover, vitamin K exists in multiple isoforms, and plasma concentrations alone may not accurately reflect overall status. The vitamin K content in the adult human liver is approximately 200–300 nmol. However, the extent to which hepatic stores represent systemic vitamin K status is uncertain, as the liver may or may not provide adequate amounts when dietary intake is insufficient.

Vitamin K2 intake can also be evaluated using Food Frequency Questionnaires (FFQ), but assessing functional activity rather than intake may be more clinically meaningful. This can be done by measuring undercarboxylated vitamin K–dependent proteins, such as osteocalcin (OCN). The extent of γ-carboxylation of OCN appears to be responsive to vitamin K intake,

potentially offering a relative indicator of vitamin K status. However, concerns remain regarding the sensitivity and specificity of this method, due to physiological fluctuations in circulating OCN levels and the lack of standardization across laboratories.

Prothrombin time (PT), a coagulation test, may also reflect vitamin K deficiency. While deficiency is rare, it can occur due to the use of certain medications including vitamin K antagonists, specific antibiotics, and anticonvulsants, as well as in liver or pancreatic disorders. Older adults are particularly at risk, likely due to diminished endogenous production of vitamin K2. This may be related to reduced peripheral conversion of K1 to K2 or decreased bacterial synthesis in the gut, as also observed in individuals with obesity or diabetes.[2]

Vitamin K Requirements and Body Stores

Vitamin K stores in the body are relatively limited, likely due to their rapid depletion without consistent dietary intake. Because vitamin K is available from various sources, vitamin K deficiency is a rare condition in adult humans.

It is estimated that the majority of vitamin K consumed is cleared from the body within 24 h. The endogenous production of K2 varies depending on the type and distribution of intestinal bacteria, making its precise contribution to daily vitamin K requirements unclear. In contrast, a reduced intake of K1 appears to be associated with inadequate vitamin K status. According to the National Academy of Sciences, the recommended dietary intake ranges from 2 mcg/day in newborns to 75 mcg/day in adolescents and remains the same for both sexes up to that age. For adults, the recommended intake is 120 mcg/day for males and 90 mcg/day for females. However, these amounts are often insufficient to maintain optimal vitamin K levels, which may vary depending on factors such as age and ethnic background.[2]

Bioavailability and Absorption of Vitamin K

The bioavailability of vitamin K varies depending on its form. Phylloquinone (K1) derived from green vegetables tends to be less bioavailable, as it is tightly bound to cell membranes. In contrast, K1 from plant oils or dietary supplements is more readily absorbed. Menaquinones (K2), primarily obtained from animal-derived foods, are typically consumed within fatty matrices, which may facilitate absorption and result in greater bioavailability compared to phylloquinone. The bioavailability of K2 is also influenced by the length of its side chain. A positive correlation has been observed between lipophilicity, bioavailability, and side chain length, which is determined by specific gut microbiota. The intestinal absorption of vitamin K follows a well-characterized mechanism similar to that of other dietary lipids, involving bile salt- and pancreatic enzyme-mediated solubilization, uptake of mixed micelles by enterocytes, incorporation into chylomicrons, and subsequent transport through the lymphatic system. However, these processes do not occur in the colon, where most menaquinones are synthesized, suggesting that absorption of these forms may be limited. Nonetheless, further research is needed to quantify differences in absorption, bioavailability, and tissue distribution between various menaquinones and phylloquinone. [2 ,3]

The Vitamin K Cycle

The vitamin K cycle is a crucial biochemical pathway that enables the post-translational γ-carboxylation of specific glutamate residues in VKDPs, converting them into γ-

carboxyglutamate (Gla) residues. This modification is essential for the functional activity of several proteins involved in coagulation, including factors II, VII, IX, and X, as well as natural anticoagulants such as protein C, protein S, and protein Z. The cycle relies on a reduced form of vitamin K (KH_2), carbon dioxide, and molecular oxygen, and is catalyzed by the enzyme γ-glutamyl carboxylase (GGCX). During the carboxylation process, KH_2 is oxidized to vitamin K 2,3-epoxide (KO), which is subsequently recycled back to its active form through a two-step reduction involving vitamin K epoxide reductase (VKOR) and a still-unidentified vitamin K reductase (VKR). GGCX and VKOR are both integral membrane proteins thought to operate in a coordinated manner, ensuring efficient redox cycling of membrane-bound vitamin K. This tightly regulated cycle not only supports the biological activity of VKDPs but also serves as an intracellular salvage mechanism, preserving limited cellular stores of vitamin K. The physiological significance of this recycling pathway is underscored by clinical observations in newborns with VKOR deficiency, who often exhibit severe coagulopathies and skeletal abnormalities [2, 4].

Vitamin K and Coagulation

Vitamin K plays a central role in blood coagulation by facilitating the γ-carboxylation of both procoagulant and anticoagulant proteins. The enzyme γ-glutamyl carboxylase utilizes vitamin K hydroquinone to convert clotting factors II, VII, IX, and X as well as proteins C and S into their active γ-carboxyglutamate forms, which are essential for binding calcium and participating in the coagulation cascade. [5, 6]

Insufficient vitamin K, whether due to dietary limitations, impaired absorption, or disrupted recycling by the VKOR complex, leads to the accumulation of undercarboxylated proteins and prolongation of prothrombin time (PT), thereby increasing the risk of bleeding [7]. Infants are particularly susceptible to this deficiency, which can manifest as classic and late onset vitamin K deficiency bleeding and may result in intracranial hemorrhage with significant risk of death or neurologic damage; this is especially common in exclusively breastfed infants, those receiving antibiotics, or those experiencing cholestatic conditions. In critical illness, adults also face subclinical vitamin K deficiency, which is associated with elevated PIVKA-II levels, hypoprothrombinemia, prolonged hospitalization, bleeding complications, and increased mortality. [5, 6]

Vitamin K Deficiency in Infants

Vitamin K deficiency in infants is associated with a condition referred to as vitamin K deficiency bleeding (VKDB), previously known as haemorrhagic disease of the newborn (HDN). It manifests in three clinical forms: early, classical, and late. The early-onset form appears within the first 24 hours of life and is typically linked to maternal medication use such as anticonvulsants or anticoagulants; it cannot be prevented by neonatal vitamin K supplementation. The classical form develops between the first and seventh day of life and is most often related to insufficient prophylaxis. The late form usually occurs between the second week and the third month of life, though it may appear up to six months of age. It predominantly affects exclusively breastfed infants and may present with cutaneous, gastrointestinal, or intracranial bleeding. Newborns are particularly vulnerable to vitamin K deficiency due to poor placental transfer of the vitamin, the lack of intestinal microbiota necessary for menaquinone

synthesis, and an immature hepatic system. Preterm infants are considered at even greater risk due to delayed enteral feeding, increased hepatic immaturity, and slower colonization of the gut. These factors underline the importance of early and adequate postnatal vitamin K supplementation, which is now a standard prophylactic measure aimed at preventing VKDB. [8]

Effects of Vitamin K on Bone Health and Osteocalcin Activation

Vitamin K, a fat-soluble vitamin, exists predominantly as phylloquinone (vitamin K1) found in green leafy vegetables and menaquinones (vitamin K2) synthesized by intestinal microbiota and found in fermented foods. While its role in coagulation is well established, recent scientific interest has turned toward its critical functions in bone metabolism, particularly through the carboxylation of osteocalcin, a vitamin K-dependent protein synthesized by osteoblasts [9].

Vitamin K and Osteocalcin Activation

Osteocalcin is one of the most abundant non-collagenous proteins in the bone matrix and is essential for bone mineralization. Vitamin K acts as a coenzyme for γ-glutamyl carboxylase, enabling the post-translational carboxylation of osteocalcin. This modification allows osteocalcin to bind calcium effectively and integrate it into the hydroxyapatite crystals of the bone matrix [10]. Without sufficient vitamin K, osteocalcin remains undercarboxylated, which is a marker of poor bone health and increased fracture risk [9].

Influence on Bone Health

Vitamin K contributes to bone health by influencing several processes:

1. **Bone Mineral Density (BMD)**: Epidemiological and interventional studies have suggested that vitamin K may preserve or increase BMD, particularly in postmenopausal women [11, 3]. However, while some trials indicate beneficial effects, others show mixed or inconclusive results, necessitating further long-term research.
2. **Fracture Prevention**: Multiple studies associate low vitamin K intake or low plasma levels with higher risks of fractures, independent of BMD. This is thought to be due to poorer bone quality related to inadequate osteocalcin activation and higher bone turnover [9, 12].
3. **Bone Remodeling**: Vitamin K appears to favor bone formation while inhibiting bone resorption. It reduces osteoclastogenesis and supports the transition of osteoblasts to osteocytes [3].

Synergy with Other Nutrients

Vitamin K does not act in isolation. Its interplay with vitamin D is particularly significant. Vitamin D promotes the synthesis of osteocalcin, but vitamin K is needed to activate it. Studies suggest that optimal bone health outcomes, including calcium metabolism and reduced fracture risk, occur when both vitamins are adequately supplied [10].

Experimental and Clinical Findings

Animal studies, such as the one combining vitamin K and teriparatide in ovariectomized rats, have demonstrated that vitamin K significantly enhances osteoblastic activity and reduces bone resorption. This leads to improved bone strength and density beyond what is achieved by monotherapy [13]. Clinically, vitamin K2 has shown promise in reducing vertebral fractures and enhancing BMD in Japanese populations [3].

Cardiovascular implications

Vitamin K plays a crucial role in inhibiting vascular calcification through the activation of Matrix Gla Protein (MGP), a vitamin K–dependent inhibitor of calcium deposition in blood vessels. In patients with end-stage kidney disease (ESKD) on hemodialysis, vitamin K deficiency is common and contributes to the progression of vascular calcification [14]. A study by Nigwekar et al. found that patients with calciphylaxis had significantly lower relative levels of carboxylated MGP (cMGP) compared to controls, indicating impaired MGP activation due to vitamin K deficiency [15].

The iPACK-HD trial was designed to test whether vitamin K1 supplementation could slow coronary artery calcification in ESKD patients. Participants receive supplementation 10 mg thrice weekly for 12 months, with outcomes measured via coronary artery calcium (CAC) scores [14].

These findings suggest that improving vitamin K status may be a promising strategy to reduce vascular calcification and cardiovascular risk in dialysis patients.

Observational studies reviewed by van Ballegooijen and Beulens show that high levels of uncarboxylated MGP, indicating low vitamin K status, correlate with increased vascular calcification, arterial stiffness, and adverse cardiovascular outcomes.[16].

In the Multi-Ethnic Study of Atherosclerosis (MESA), Vitamin K-dependent protein (VKDP) activity was measured via Des-gamma-carboxy prothrombin (DCP) levels, where higher DCP levels indicated lower vitamin K activity. The study found that individuals with higher DCP concentrations had a significantly increased risk of ischemic cardiovascular events over an 11-year follow-up. These results were independent of traditional CVD risk factors and vitamin K intake, suggesting a robust link between VKDP inactivity and cardiovascular risk [17].

A comprehensive meta-analysis by Lees et al. examined the effects of vitamin K on vascular calcification and arterial stiffness. The analysis of 13 clinical trials and 14 longitudinal studies concluded that vitamin K supplementation significantly reduced vascular calcification and levels of inactive MGP, though effects on arterial stiffness were less consistent. Importantly, higher levels of inactive VKDPs were associated with increased cardiovascular events and mortality, reinforcing the potential clinical utility of vitamin K [18].

Neurological Functions of Vitamin K

Among menaquinones (K2) forms, menaquinone-4 (MK-4) is particularly enriched in the brain, mainly in the cortex and cerebellum. A theory has been proposed suggesting that MK-4 crosses the blood-brain barrier and accumulates in neural tissues. MK-4 may help keep the brain healthy by supporting sfingolipids metabolism and helping control specific proteins like Gas6 and Protein S, which are vitamin K dependent proteins, that protect nerve cells and help them survive [19], [20]. Vitamin K may have a dual role, providing neuroprotection and neurodegenerative proccess.

Neuroprotective Mechanisms of Vitamin K

Vitamin K, especially its K2 form known as menaquinone-4 (MK-4), plays several important roles in protecting brain health. A primary function is to support the biosynthesis of sphingolipids, which are essential components of neuronal membranes. These include ceramides, sulfatides, and gangliosides, which help maintain the structure of neurons and enable communication between them [21].

In addition, Vitamin K has antioxidant and anti-inflammatory properties. It helps reduce oxidative stress by lowering the production of reactive oxygen species (ROS), which can damage brain cells. In addition, MK-4 appears to regulate microglial activity which can help calm inflammation in the nervous system [21, 22].

Another important mechanism involves vitamin K dependent proteins (VKDPs) such as Gas6 and Protein S. These proteins need vitamin K for a chemical process called carboxylation, which allows them to function properly. In the brain, they help neurons survive, promote repair processes, and protect against programmed cell death [19, 20, 21].

By supporting antioxidant defenses, regulating inflammation, and enabling vital proteins to function, vitamin K helps preserve brain function and protect neurons as we age or face disease. These combined effects may slow or reduce the risk of developing neurodegenerative conditions. Disruptions in vitamin K-related pathways, such as sphingolipid metabolism, have been linked to disorders like Alzheimer's disease [19, 20, 21, 22].

Vitamin K and Neurodegenerative Disorders

Alzheimer's Disease and Dementia

Post-mortem studies have shown that individuals with higher MK-4 concentrations in brain tissue tend to have fewer signs of Alzheimer's pathology, such as neurofibrillary tangles. These individuals also performed better scores on global cognitive assessments shortly before death [19]. Additionally, cross-sectional analyses have found that people in the early stages of Alzheimer's disease often have significantly lower levels of circulating phylloquinone (vitamin K1) compared to healthy controls [19, 20].

Preliminary evidence from animal models suggests that MK-4 may inhibit α-synuclein aggregation, a pathological hallmark of Parkinson's disease, and support remyelination processes relevant in multiple sclerosis [21]. The antioxidant and anti-inflammatory roles of MK-4 further support its potential in reducing the progression of neurodegeneration.

Use of vitamin K antagonists (VKAs), such as warfarin, has been associated with cognitive decline in older adults, particularly affecting executive functions. Longitudinal human studies have reported significant reductions in Frontal Assessment Battery (FAB) scores over 24-month periods in VKA users, accompanied by neuroimaging evidence of reduced frontal lobe volume [23]. These findings suggest a potential link between impaired vitamin K metabolism and neurodegeneration. Supporting this, animal studies have shown that VKA exposure leads to brain MK-4 depletion and results in cognitive impairment, lower locomotor activity, and exploratory behavior, further reinforcing the role of vitamin K in maintaining cognitive function and brain integrity [22].

Emerging role in the dopaminergic system in research on rats indicates that vitamin K deficiency particularly when caused by warfarin use may disrupt dopamine metabolism in the brain. These changes were linked to altered movement and memory performance under vitamin K deficient conditions [22]. While these results are preliminary, they indicate a possible interaction between vitamin K and dopaminergic pathways relevant to Parkinson's disease and mood disorders.

Cognitive Function and Population Studies

Observational studies show that higher dietary intake of vitamin K correlates with better cognitive tests and reduced subjective memory complaints [19, 20, 23]. For instance, Soutif-Veillon et al. (2016) found that older adults with increased Vitamin K intake has been correlated with a lower incidence and intensity of subjective memory problems [20].

Vitamin K and Chronic Diseases

The collective evidence from multiple observational and interventional studies underscores its impact on cardiovascular health, pulmonary function, neurodegeneration, cancer risk, and musculoskeletal disorders.

Pulmonary Function

A large cross-sectional study demonstrated that low vitamin K status, reflected by high dephosphorylated-uncarboxylated MGP (dp-ucMGP), correlates with reduced lung function parameters (FEV1 and FVC) and a higher prevalence of chronic respiratory conditions such as asthma and COPD [24]. These data highlight a possible mechanistic link between vitamin K and lung tissue integrity through its influence on elastin fiber preservation and calcification inhibition.

Neurodegenerative Diseases

Vitamin K's role in cognitive function has gained increasing attention. Menaquinone-4 (MK-4), the primary form found in the brain, was associated with lower odds of dementia, milder Alzheimer's disease pathology, and slower cognitive decline in participants from the Rush Memory and Aging Project [25]. Additionally, stability studies confirm that MK-4 concentrations in brain tissues are reliable for up to 9 years of freezer storage, validating the biomarker's utility [26].

Osteoarthritis

Cartilage calcification, a hallmark of osteoarthritis (OA), is influenced by the activity of VKDPs such as MGP and Gla-rich protein (GRP). Observational data suggest that low circulating vitamin K levels are associated with increased cartilage degradation, higher The Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores, and reduced cartilage thickness [27]. Mechanistic studies demonstrate vitamin K's capacity to inhibit bone morphogenetic protein-mediated calcification, suggesting a protective role against OA progression.

Cancer

Data from the Japan Collaborative Cohort Study suggest an inverse relationship between dietary vitamin K intake and lung cancer risk. The highest quartile of vitamin K intake was associated with a significantly reduced hazard ratio for lung cancer, particularly among men and current smokers [28]. These findings align with in vitro and animal studies that identify vitamin K as an inhibitor of cancer cell proliferation and promoter of apoptosis.

Gastrointestinal Health

Beyond its systemic roles, vitamin K contributes to gut health by modulating inflammation, oxidative stress, and microbiota composition. Its deficiency is frequently observed in patients with inflammatory bowel diseases (IBDs), and supplementation may alleviate symptoms and promote epithelial repair [29].

Drug Interactions and Supplementation

Drug Interactions with Vitamin K

One of the most clinical example is the interaction between vitamin K and vitamin K antagonists (VKAs), such as warfarin. Warfarin acts by inhibiting the vitamin K epoxide reductase complex, effectively reducing the regeneration of active vitamin K and thereby impairing γ-carboxylation of VKDPs necessary for clotting factors II, VII, IX, and X [30]. Consequently, fluctuations in dietary vitamin K intake can lead to instability in anticoagulation control, measured by the international normalized ratio (INR).
A systematic review confirmed that numerous dietary items including spinach, green tea, cranberry, and herbal supplements such as Ginkgo biloba can significantly alter warfarin's effects [30]. However, another meta-analysis emphasized that stability in vitamin K intake, rather than strict restriction, contributes more to consistent anticoagulation outcomes [31].

Other Drug Interactions

The review by Tan and Li (2024) elaborated on the shared metabolic and transport pathways of vitamin K and cholesterol, indicating that lipid-lowering drugs like statins can interfere with vitamin K metabolism by inhibiting shared pathways such as NPC1L1 and ABCG5/8 transporters [32]. Furthermore, anticonvulsants like carbamazepine and certain antibiotics have been shown to impair vitamin K metabolism in pregnant women, posing risks of hemorrhage to both mother and fetus [33].

Supplementation in Specific Populations

Newborns

Vitamin K deficiency bleeding is a potentially fatal condition in newborns. Without prophylaxis, the risk is approximately 1 in 59 births; this risk is reduced to 1 in 100,000 with intramuscular administration of vitamin K at birth [34]. Oral or maternal supplementation is significantly less effective, and rising trends in parental refusal of prophylaxis have resulted in regional Vitamin K bleeding outbreaks.

Pregnant Women

The systematic review on vitamin K supplementation during pregnancy concluded that while maternal plasma vitamin K1 levels improve with supplementation, there is insufficient evidence that this prevents neonatal bleeding or affects other outcomes such as perinatal mortality or maternal bleeding [33]. Quality of evidence across trials was generally low, and more rigorous studies are needed.

Elderly Adults

A randomized controlled trial on older adults receiving vitamin D supplementation showed that vitamin D alone may alter levels of undercarboxylated matrix Gla protein (dp-ucMGP), a biomarker of vitamin K status [35]. This highlights the possible interplay between vitamins D and K in regulating vascular calcification and bone health.

Vitamin K and Cardiovascular Disease

Matrix Gla protein (MGP) is a potent inhibitor of vascular calcification, and its activity is vitamin K-dependent. Clinical trials assessing vitamin K supplementation (K1 and K2) for cardiovascular protection have yielded mixed results. While supplementation consistently improves MGP carboxylation, this biochemical improvement does not always translate into reduced vascular calcification or arterial stiffness [36].
Some studies indicate benefits for patients with pre-existing vascular calcification, but the overall evidence does not yet support broad use of vitamin K for cardiovascular disease prevention [36].

Microbiota and Bioavailability

Recent findings reveal that the gut microbiota plays a critical role in modulating the bioavailability of vitamin K. Microorganisms in the colon can convert dietary vitamin K1 into various menaquinones, which are differently absorbed and have unique tissue distribution profiles [37]. Disruptions to gut microbiota, such as through antibiotic use or disease, can therefore impact vitamin K status.

Conclusion

Vitamin K, in its two principal forms, phylloquinone (K1) and menaquinones (K2), is a biologically essential compound with a wide range of functions in human physiology. While its role in hepatic synthesis of coagulation factors is well established and historically recognized, recent scientific evidence emphasizes its involvement in numerous extrahepatic processes that are critical to overall health.

Research increasingly supports the contribution of vitamin K to cardiovascular integrity, bone metabolism, and neurological function. In particular, menaquinone-4 (MK-4) has demonstrated potential neuroprotective effects by supporting lipid membrane stability, reducing oxidative stress, modulating inflammation, and regulating vitamin K-dependent neuroproteins. These mechanisms may be relevant to the prevention or slowing of cognitive decline and neurodegenerative conditions, particularly in the aging population.

Vitamin K also plays an important role in modulating vascular calcification, primarily through the activation of matrix Gla protein. This action is especially relevant in individuals with chronic kidney disease and in elderly adults, where deficiency may exacerbate cardiovascular risks. The influence of vitamin K on skeletal health, mediated through the carboxylation of osteocalcin, also suggests a protective effect against osteoporosis and fractures.

Furthermore, vitamin K interacts with various medications, most notably anticoagulants such as warfarin, which require careful dietary and pharmacological management. Supplementation is clearly beneficial in newborns, where it effectively prevents life-threatening deficiency bleeding. However, in other populations, current evidence supports a selective, risk-based approach to supplementation rather than broad recommendations for universal use.

In conclusion, vitamin K should be recognized not only as a coagulation cofactor but also as a key regulator of multiple physiological systems. Maintaining adequate vitamin K status through a balanced diet and, where appropriate, targeted supplementation may offer significant benefits for health maintenance and chronic disease prevention. Continued research is warranted to further define optimal intake levels, refine assessment methods, and clarify the full therapeutic potential of this essential nutrient.

Disclosure

Author's contribution

Conceptualization: Michał Wycik

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REFERENCES

[1] P. Mladěnka et al., "Vitamin K - sources, physiological role, kinetics, deficiency, detection, therapeutic use, and toxicity," Nutr Rev, vol. 80, no. 4, pp. 677–698, Apr. 2022, doi: 10.1093/NUTRIT/NUAB061,.

[2] M. J. Shearer, X. Fu, and S. L. Booth, "Vitamin K Nutrition, Metabolism, and Requirements: Current Concepts and Future Research," Advances in Nutrition, vol. 3, no. 2, pp. 182–195, Mar. 2012, doi: 10.3945/AN.111.001800.

[3] A. Palermo et al., "Vitamin K and osteoporosis: Myth or reality?," Metabolism, vol. 70, pp. 57–71, 2017, doi: 10.1016/j.metabol.2017.01.032.

[4] J. K. Tie and D. W. Stafford, "Structural and functional insights into enzymes of the vitamin K cycle," Journal of Thrombosis and Haemostasis, vol. 14, no. 2, pp. 236–247, Feb. 2016, doi: 10.1111/JTH.13217/ASSET/A04B48AF-EC0A-4F6F-B1D8-8FF3874BF498/MAIN.ASSETS/JTH13217-FIG-0005-M.JPG.

[5] S. Araki and A. Shirahata, "Vitamin k deficiency bleeding in infancy," Nutrients, vol. 12, no. 3, Mar. 2020, doi: 10.3390/NU12030780,.

[6] M. C. Paulus, M. Drent, I. W. K. Kouw, M. G. J. Balvers, A. Bast, and A. R. H. van Zanten, "Vitamin K: a potential missing link in critical illness–a scoping review," Crit Care, vol. 28, no. 1, p. 212, Dec. 2024, doi: 10.1186/S13054-024-05001-2.

[7] M. Elalfy, K. Eltonbary, O. Elalfy, M. Gadallah, A. Zidan, and H. Abdel-Hady, "Intracranial haemorrhage associated with Vitamin K deficiency in Egyptian infants," Acta Paediatrica, International Journal of Paediatrics, vol. 110, no. 11, pp. 2937–2943, Nov. 2021, doi: 10.1111/APA.16011,.

[8] S. Jullien, “Vitamin K prophylaxis in newborns,” BMC Pediatr, vol. 21, no. 1, pp. 1–7, Sep. 2021, doi: 10.1186/S12887-021-02701-4/TABLES/5.
[9] A. O. Elshaikh, L. Shah, C. J. Mathew, R. Lee, M. T. Jose, and I. Cancarevic, “Influence of Vitamin K on Bone Mineral Density and Osteoporosis,” Cureus, vol. 12, no. 10, p. e10816, Oct. 2020, doi: 10.7759/CUREUS.10816.
[10] J. O. Aaseth, T. E. Finnes, M. Askim, and J. Alexander, “The Importance of Vitamin K and the Combination of Vitamins K and D for Calcium Metabolism and Bone Health: A Review,” Nutrients 2024, Vol. 16, Page 2420, vol. 16, no. 15, p. 2420, Jul. 2024, doi: 10.3390/NU16152420.
[11] M. Fusaro et al., “Vitamin K and Osteoporosis,” Nutrients, vol. 12, no. 12, p. 3625, Dec. 2020, doi: 10.3390/NU12123625.
[12] G. K. Schwalfenberg, “Vitamins K1 and K2: The Emerging Group of Vitamins Required for Human Health,” J Nutr Metab, vol. 2017, no. 1, p. 6254836, Jan. 2017, doi: 10.1155/2017/6254836.
[13] Y. Huang, “Combined treatment of vitamin K and teriparatide on bone metabolism and biomechanics in rats with osteoporosis,” Exp Ther Med, vol. 15, no. 1, p. 315, Jan. 2017, doi: 10.3892/ETM.2017.5420.
[14] R. M. Holden et al., “Inhibiting the progression of arterial calcification with vitamin K in HemoDialysis patients (iPACK-HD) trial: Rationale and study design for a randomized trial of vitamin K in patients with end stage kidney disease,” Can J Kidney Health Dis, vol. 2, no. 1, May 2015, doi: 10.1186/s40697-015-0053-x.
[15] S. U. Nigwekar et al., “Vitamin K-Dependent carboxylation of matrix gla protein influences the risk of calciphylaxis,” Journal of the American Society of Nephrology, vol. 28, no. 6, pp. 1717–1722, Jun. 2017, doi: 10.1681/ASN.2016060651.
[16] A. J. van Ballegooijen and J. W. Beulens, “The Role of Vitamin K Status in Cardiovascular Health: Evidence from Observational and Clinical Studies,” Sep. 01, 2017, Current Science Inc. doi: 10.1007/s13668-017-0208-8.
[17] J. Danziger et al., “Vitamin K-dependent protein activity and incident ischemic cardiovascular disease: The multi-ethnic study of atherosclerosis,” Arterioscler Thromb Vasc Biol, vol. 36, no. 5, pp. 1037–1042, May 2016, doi: 10.1161/ATVBAHA.116.307273.
[18] J. S. Lees, F. A. Chapman, M. D. Witham, A. G. Jardine, and P. B. Mark, “Vitamin K status, supplementation and vascular disease: A systematic review and meta-analysis,” Heart, vol. 105, no. 12, pp. 938–945, Jun. 2019, doi: 10.1136/heartjnl-2018-313955.
[19] S. L. Booth et al., “Association of vitamin K with cognitive decline and neuropathology in community-dwelling older persons,” Alzheimer’s & Dementia: Translational Research & Clinical Interventions, vol. 8, no. 1, p. e12255, Jan. 2022, doi: 10.1002/TRC2.12255.
[20] A. Kiely, G. Ferland, B. Ouliass, P. W. O’Toole, H. Purtill, and E. M. O’Connor, “Vitamin K status and inflammation are associated with cognition in older Irish adults,” Nutr Neurosci, vol. 23, no. 8, pp. 591–599, Aug. 2020, doi: 10.1080/1028415X.2018.1536411.
[21] E. Emekli-Alturfan and A. A. Alturfan, “The emerging relationship between vitamin K and neurodegenerative diseases: a review of current evidence,” Molecular Biology Reports 2022 50:1, vol. 50, no. 1, pp. 815–828, Nov. 2022, doi: 10.1007/S11033-022-07925-W.
[22] S. Tamadon-Nejad, B. Ouliass, J. Rochford, and G. Ferland, “Vitamin K deficiency induced by warfarin is associated with cognitive and behavioral perturbations, and alterations in brain sphingolipids in rats,” Front Aging Neurosci, vol. 10, no. JUL, Jul. 2018, doi: 10.3389/FNAGI.2018.00213/FULL.

[23] A. Soutif-Veillon et al., “Increased dietary vitamin K intake is associated with less severe subjective memory complaint among older adults,” Maturitas, vol. 93, pp. 131–136, Nov. 2016, doi: 10.1016/J.MATURITAS.2016.02.004.
[24] T. Jespersen et al., “The association of vitamin K status with lung function and disease in a general population,” ERJ Open Res, vol. 9, no. 5, Sep. 2023, doi: 10.1183/23120541.00208-2023.
[25] S. L. Booth et al., “Association of vitamin K with cognitive decline and neuropathology in community-dwelling older persons,” Alzheimer’s and Dementia: Translational Research and Clinical Interventions, vol. 8, no. 1, 2022, doi: 10.1002/trc2.12255.
[26] X. Fu et al., “Vitamin D and Vitamin K Concentrations in Human Brain Tissue Are Influenced by Freezer Storage Time: The Memory and Aging Project,” Journal of Nutrition, vol. 151, no. 1, pp. 104–108, Jan. 2021, doi: 10.1093/jn/nxaa336.
[27] K. Y. Chin, “The relationship between vitamin k and osteoarthritis: A review of current evidence,” Nutrients, vol. 12, no. 5, May 2020, doi: 10.3390/nu12051208.
[28] F. Yan, E. S. Eshak, A. Arafa, A. Tamakoshi, and H. Iso, “Vitamin K Intake and Risk of Lung Cancer: The Japan Collaborative Cohort Study,” J Epidemiol, vol. 33, no. 10, pp. 536–542, 2023, doi: 10.2188/jea.JE20220063.
[29] Y. Lai, H. Masatoshi, Y. Ma, Y. Guo, and B. Zhang, “Role of Vitamin K in Intestinal Health,” Jan. 05, 2022, Frontiers Media S.A. doi: 10.3389/fimmu.2021.791565.
[30] C. S. S. Tan and S. W. H. Lee, “Warfarin and food, herbal or dietary supplement interactions: A systematic review,” Br J Clin Pharmacol, vol. 87, no. 2, pp. 352–374, Feb. 2021, doi: 10.1111/BCP.14404;PAGEGROUP:STRING:PUBLICATION.
[31] F. Violi, G. Y. H. Lip, P. Pignatelli, and D. Pastori, “Interaction between dietary Vitamin K intake and anticoagulation by Vitamin K antagonists: is it really true?: A systematic review,” Medicine (United States), vol. 95, no. 10, Mar. 2016, doi: 10.1097/MD.0000000000002895.
[32] J. Tan and Y. Li, “Revisiting the interconnection between lipids and vitamin K metabolism: insights from recent research and potential therapeutic implications: a review,” Dec. 01, 2024, BioMed Central Ltd. doi: 10.1186/s12986-023-00779-4.
[33] S. Shahrook, E. Ota, N. Hanada, K. Sawada, and R. Mori, “Vitamin K supplementation during pregnancy for improving outcomes: a systematic review and meta-analysis,” Sci Rep, vol. 8, no. 1, Dec. 2018, doi: 10.1038/s41598-018-29616-y.
[34] J. C. Phillippi, S. L. Holley, A. Morad, and M. R. Collins, “Prevention of Vitamin K Deficiency Bleeding,” J Midwifery Womens Health, vol. 61, no. 5, pp. 632–636, Sep. 2016, doi: 10.1111/jmwh.12470.
[35] A. J. van Ballegooijen et al., “Effect of 6-Month Vitamin D Supplementation on Plasma Matrix Gla Protein in Older Adults,” Nutrients 2019, Vol. 11, Page 231, vol. 11, no. 2, p. 231, Jan. 2019, doi: 10.3390/NU11020231.
[36] C. Vlasschaert, C. J. Goss, N. G. Pilkey, S. McKeown, and R. M. Holden, “Vitamin K Supplementation for the Prevention of Cardiovascular Disease: Where Is the Evidence? A Systematic Review of Controlled Trials,” Nutrients 2020, Vol. 12, Page 2909, vol. 12, no. 10, p. 2909, Sep. 2020, doi: 10.3390/NU12102909.
[37] J. L. Ellis et al., “Dietary vitamin K is remodeled by gut microbiota and influences community composition,” Gut Microbes, vol. 13, no. 1, pp. 1–16, 2021, doi: 10.1080/19490976.2021.1887721.