Could Vitamin K Affect Cognition: Current Evidences

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Abstract

Background: Vitamin K is a fat-soluble nutrient mainly found in green leafy vegetables as phylloquinone (Vitamin K1). This vitamin is widely known for its procoagulant effect. It acts as a cofactor for the enzyme that allows the activation of vitamin K-dependent factors (II, VII, IX, X, protein C, and protein S). A recent review collected studies that show its involvement in the metabolism of the central nervous system (CNS), suggesting the possibility that a vitamin K deficiency might be related to the onset of cognitive impairment. Dementia can be defined as a clinical syndrome of mental capacity characterized by a substantial global decline in cognitive function that is not attributable to altered consciousness; it consists of a combination of symptoms attributable to various causes or pathological events. Cognitive impairment is a definition used in this review to indicate alterations in multiple cognitive domains highlightable with standardized tests, as clinically manifest dementia is often preceded by a heterogeneous spectrum of cognitive performances. Studies proved that vitamin K deficiency has a role in the pathogenesis of neurodegenerative diseases. Furthermore, Vitamin K1 and K2 have been shown to prevent oxidative injury to developing oligodendrocytes and neurons.

Keywords: Vitamin K, Cognition.

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Background

The original term vitamin "K" comes from the K in the Germanic word "Koagulation" meaning the ability to clot blood or prevent hemorrhage. In 1929, the Danish Dr. Henrik Dam discovered vitamin k role in blood coagulation and was awarded the Nobel Prize in Physiology in 1943 with the American Dr. Edward A, doisy **(1).**

*Vitamin k family (Naphthaquinone):

Vitamin K is subdivided into three subfamilies: vitamin K1 (Phylloquinone), vitamin K2 (Menaquinones) and Vitamin K3 (Menadione) which is synthetic, highly toxic and banned by food and Drug Administration (FDA). All the K vitamins have a similar the "quinone" ring and a different isoprenoid side chain **(2,3).**

Phylloquinone contains a phytyl side chain which forms 4 prenyl units. Menaquinones are classified according to the length of their side chain and are named as MK-n, where n represents the number of isoprenoid residues in that chain **(3).**

Thus, MK-7 contains seven isoprenoid units. MK-7 is more lipophilic than K1 and MK-4, resulting in a much longer half-life **(4).**

***Vitamin K2 (Menaquinones):**

Vitamin K2 can be divided into subtypes, according to the number of prenyl units to short-chain (i.e., menaquinone-4; MK-4) and long-chain (i.e., MK-7, MK-8, and MK-9). **(3, 5).**

***Synthesis:**

Mammals cannot synthesize new vitamin K2 but convert vitamin K1 into MK-4 a form of vitamin K2 by UbiA prenyltransferase domain containing protein l(UBIAD1**) (6).**

*** Recommended daily intake (RDI**):

There is no certain daily intake dose till now. The recommended range from 5 to 600 μg/. The intake of vitamin K2 from food corresponds to only 25%. Therefore, administration of K2 supplements in a high dosage is recommended for meeting the required daily **(7).**

***Bioavailability:**

Menaquinones are not equally well absorbed. MK-7 is absorbed most efficiently and has the greatest bioavailability **(4).** Long chain menaquinones, such as MK-7 and MK-9 have longer half-life **(4).**and available longer in the circulation for several days to be absorbed by extra hepatic tissue **(4).**MK-9 is more lipophilic, has a very long half-life, it is poorly absorbed due to the lipophilicity **(4).**

***Uptake and Distribution:**

All vitamin K forms can be taken up by enterocytes in the small intestine and packaged into chylomicrons during absorption. Then chylomicrons are taken up by the liver. Then, vitamin K2 particularly long chain derivatives are redistributed to the circulation to be available for extra-hepatic tissues such as bone and vasculature **(4).**

***Mechanisms of action:**

Vitamin K1, 2 play a critical role as a co-factor for γ-glutamyl carboxylase-catalyzed reactions in the post translational carboxylation of glutamic acid to γ-carboxy glutamic acid **(3).** These γ-carboxy glutamate (Gla) residues form calcium-binding sites that are essential for the activity of the proteins in which they are found **(8).** As far as known, 20 human proteins are found to be γ-carboxylated **(9)**

Vitamin K and Neurological Disease:

Many of vitamin K2 dependent proteins are highly expressed in the brain and have protective effect of K2 on neurons **(10, 11).).**MK-4 improved energy production and prevented mutation which is characteristic of Parkinson's disease **(12).** Moreover, various K2 analogs have been found to be important in neuronal differentiation **(13).** A study involved patients with multiple sclerosis (MS), K2 levels were greatly reduced in patients with MS **(14).** Also, K2 levels were correlated with neurological spasms and lesions of the optic nerves which indicates the important role for vitamin K2 in neurological disease **(15)**

MK-7playcritical role in the synthesis of sphingolipids in the brain **(16).**Vitamin K dependent proteins such as Protein Gas6 gene have been shown to play grat role inthe peripheral and central nervous system **(17).**Interestingly, Vitamin K may have a role in the pathogenesis of Alzheimer's disease through its regulatory role in sulfo transferase activity and growth factor/tyrosine kinase receptor activity in the

brain**(18).**Intake of vitamin K may improve cognitive function in healthy older adults. So, vitamin K antagonists' usage has been associated with more cognitive disorders **(19).**

Moreover, Vitamin K2 can prevent the development of anxiety due to its effects on blood glucose and depression, but did not improve the memory deficit caused by the dietary manipulation in an experimental model of metabolic syndrome.In geriatrics cognition improvement is associated with higher dietary intake of vitaminK **(20).**

***Relation between osteocalcin and vitamin K2 (MK-7):**

The extra hepatic vitamin K-dependent proteins (Gla-proteins) are involved in extracellular matrix mineralization: osteocalcin, matrix Gla-protein and periostin. The ratio of OCand matrix Gla-protein circulating in their uncarboxylated forms indicates a low vitamin concentration in extra-hepatic tissues **(3).**

Serum carboxylated OC (cOC), undercarboxylated OC (ucOC) and the ratio of cOC/ucOC, all of them are sensitive marker of vitamin K status. Interestingly, the ratio of cOC/ucOC significantly decreases after two weeks of MK-7 supplementation and continues to decrease decreased further by about 40% from baseline **(21).**MK-7 is known to regulate OC gene expression in osteoblastic cells and vascular smooth muscle cell. MKs works through the steroid receptors on the nuclear membrane of osteoblastic cells acting as transcription factor **(22).**

MK-7 in addition to its well-known role in OC carboxylation, which modulates the deposition of calcium in bone, increases collagen production using osteoblasts **(23).** Collagen is essential to bone flexibility and elasticity, and responsible for matrix production, the material on which calcium and other minerals accumulate. Therefore, oc and many VKDPs, such as MGP, protein S along and periostin are critical for formation of high-quality bone. This indicates the important role of vitamin K and VKDPs in bones **(23).**

Menaquinone-7 (MK-7) is more effective than phylloquinone even if the supplementation is lower dose, but above theRDIs **(4).** Moreover, MK-7 among all vitamin K homologs has been shown to have the highest bioavailability and the most effective in OC carboxylation. Many nutrient preparations, such as enteral feeding products and multi-nutrient diets preparation result in vitamin K deficiency resulting in bone fracture risk. This throw a light on modification of the current RDIs of vitamin K set by many countries as it may be insufficient for the γ-carboxylation of OC **(23).**

Many studies found significant correlation between the end plasma MK-7 levels and the circulating levels of ucOC and dp-ucMGP. **Tsukamoto et al. (24)** found a positive relationship between serum MK-7 and cOC concentrations**. Bruge`et al. (25)** found a significant correlation between differences in plasma MK-7 and changes in the ratio of cOC:ucOC **(24, 23)**

Brain changes during menopause

"The brain fog " is the common expression for the cognitive impairment syndrome occurring during the menopause transition. It is called that because it is transient period. The woman feels a little off and muddy brain and when the transition passes, these clouds clear and the fog leaves. The cognitive function impairment varies across the menopausal transition. Early menopause is considered a critical period during which there is a decline in attention, working memory, verbal learning, verbal memory and fine motor speed **(26).**

Early in menopause, Women complain from severe dementia, when seeking psychologist, they may be diagnosed. The symptoms are common in with thyroid disease (myxedema), vitamin deficiency, liver, kidney diseases and infections, and rarely concern about the woman's menstrual history and menopause **(26).**

Studies have found that in late life the size of the hippocampus diminishes and can be used as is a predictor for memory performance. Small hippocampi are associated with increase the risk for dementia and poor memory. The association between receiving hormone replacement therapy and the variation in hippocampi volume is controversial. Some studies proved that estrogen could improve the memory by increasing hippocampi volume but other studies proved that estrogen has no effect on the volume **(27).**

The disturbed connectivity between the amygdaliod and insulin which is common during menopause is the base of the depression and sleep disorders observed in women. The cause is the insula involved in consciousness and plays a major role in diverse functions, like negative emotional experiences and regulation of body homeostasis **(28).**

Menopause is characterized by damaged visual memory which is due to disturbed activity of the occipital gyrus. Also disturbed connectivity of the parietal gyrus is involved in processing the informations associated with numbers. This leads to further disturbance of women functional memory **(29).**

The present review stems from a growing interest in the role of vitamin K in brain function, especially in cognition. It collected recent contributions to the topic, showing interesting, even though not definitive, evidence of direct correlation between vitamin K levels and cognitive performance. Moreover, VKAs might influence negatively some cognitive domains such as visual memory and verbal fluency and the brain volume. Only a small number of publications were based on studies performed on humans, limiting the amount of papers included. These studies were heterogeneous in several ways: study design, markers used to measure vitamin K levels, method used to assess cognitive performance and age of patients included in the studies. Further evidence should be gathered using more standardized methodology to foster comparability of results **(30)**.

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