



## The Anti-Inflammatory Effect of Vitamin K in Aging

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### Abstract

Vitamin K is a fundamental enzymatic co-factor implicated in the carboxylation of several vitamin K dependent proteins involved in the pathogenesis of certain age – related diseases. Inflammation is realized as an important factor in such diseases. Vitamin K is recognized to play an anti-inflammatory behavior that is distinct of its action as an enzymatic co- factor by suppressing many signaling pathways mainly the nuclear factor  $\kappa$ B (NF- $\kappa$ B) signal transduction pathway. As well as to play a role as an antioxidant versus the generation of reactive oxidative species (ROS). The purpose of this review is to focus on the protective function of vitamin K as an anti-inflammatory agent in these age- associated diseases. And the importance of vitamin K complement as a protective nutrient in aging.

**Keywords:** vitamin K, aging, inflammation, NF- $\kappa$ B, age- related diseases, inflammatory cytokines

### 1. Vitamin K Types

Vitamin K is considered as a lipid soluble vitamin and it presents in nature in two types; vitamin K1 (phylloquinone) and vitamin K2 (menaquinones) [1]. Vitamin K1 is the most current form of vitamin K found in food [2]. Vitamin K1 is mostly present in the green vegetables, whereas bacteria synthesized vitamin K2 [3]. And they are mostly present in meat, dairy and fermented food [4]. Vitamin K2 can be occurred into 2 types; short series (MK-4) and long series (MK-7, MK-8 and MK-9) [5].



## 2. Vitamin K Functions

The major role of vitamin K is in the post- translational carboxylation of specific vitamin K dependent proteins, especially proteins used in coagulation [6]. Also, some vitamin K dependent proteins possess important functions in bone metabolism and soft tissue calcification [7]. In addition, vitamin K seems to have anti-inflammatory effect that is separate of its action as enzymatic co- factor [8].

## 3. Inflammation:

Inflammation is defined as a biologic process that can be initiated by several factors such as pathogens, toxins and damaged cells. Those factors encourage acute and/ or chronic inflammation leading to a tissue harm or a disease. Infectious and non- infectious agents stimulate inflammation and activate the inflammatory signals [9]. Inflammation can be mediated by the interaction of the inflammatory cytokines with their Toll- like receptors (TLRs) such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) receptor, interleukin 1 and 6 (IL-1 and IL-6) receptors [10]. Activation of these receptors triggers many signaling routes like the nuclear factor kappa-B (NF- $\kappa$ B), mitogen-activated protein kinase (MAPK), activator of transcription (STAT) pathways and Janus kinase (JAK)-signal transducer [11,12].

## 4. Vitamin K and Inflammation:

The precise role of vitamin K in inflammation is not clear yet, but it is thought that it affects various fields such as chemokines and cytokines physiology, biology and the molecular biology of their signaling pathways [13].

The nuclear factor kappa- B (NF- $\kappa$ B) pathway is one of the important ways that participates in several functions in cells such as inflammation, cell growth, apoptosis and tumorigenesis from birth till the death of cells [14-16]. The nuclear factor kappa- B (NF- $\kappa$ B) is a group of proteins that are present as homo- and hetero- dimers [17]. This dimer is usually present silent in the cytosol of cells in association with an inhibitory protein called (I $\kappa$ B) [18]. Phosphorylation of (I $\kappa$ B) by kinase enzymes (IKK) leads to the removal of (I $\kappa$ B) and activation of (NF- $\kappa$ B) protein [19]. The (I $\kappa$ B) protein is then selected to be degraded in the proteasome [20]. The (I $\kappa$ B) protein and the (IKK) enzymes together with the (IKK) modulator system represent the center of NF- $\kappa$ B regulation and activation [21]. Recent studies suggested that vitamin K performs a major part in NF-  $\kappa$ B activation pathway, also in the regulation of the MAPK signaling pathway [22]. Previous studies stated that IL-6 synthesis is under the control of the NF- $\kappa$ B signaling pathway [23], and that this inflammatory pathway is achieved by interaction with certain receptors that can activate both the STAT and JAK signaling pathways [24].

The way by which vitamin K can influence inflammation biomarkers has not been yet known but it is thought that it might affect the gene expression of the inflammatory cytokines especially IL-6 and osteoprotegerin [25, 26]. Previous studies stated that plasma vitamin K1 concentration and vitamin K1 ingestion were in reverse relationship with both osteoprotegerin and IL-6 concentrations [27].

Furthermore, vitamin K was shown to have an alternative role as an anti-inflammatory agent by suppressing the oxidative stress caused by reactive oxidative species (ROS) [28]. For example; the reduced form of vitamin K (KH<sub>2</sub>) was considered as an antioxidant in the peroxidation of the phospholipid cell membrane [29, 30]. Vitamin K epoxide reductase complex subunit 1 (VKORC1)-like 1 (VKORC1L1) enzyme plays a major role in increasing the KH<sub>2</sub> concentration and decreasing the ROS activity intracellularly [31]. Both vitamin K1 and vitamin K2 were considered as antioxidants in preventing the death of cells caused by ROS in cultured neurons by blocking the 12-lipoxygenase (12-LOX) activation pathway [32].

### **5. Vitamin K and Aging:**

Aging is distinguished by low inflammation status [33]. An increase in the levels of TNF- $\alpha$ , IL-6 and C- reactive protein (CRP) contribute to the development of chronic age illness like osteoarthritis, cardiovascular and other chronic diseases [34- 37]. Previous studies noted a combination between decrease vitamin K level and poor cognition function [38].

Also, there are differences in the daily intake of vitamin K1 in elderly patients with Alzheimer's disease in comparison to healthy controls [39, 40]. Presse et al. (2013) stated that elderly people with intact cognition level had high concentration of serum vitamin K1 in association with increased recollection tests and verbal episodic memory [41].

More recent studies documented that elderly individuals with high vitamin K intake had better cognition and behavioral setting [42]. Similarly, several studies reported that aging and cognition decline had been correlated with inflammation and increased inflammatory cytokines [43-45].

Wichmann et al. (2014) found that patients suffering from cognition impairment had higher levels of IL-6 [46]. Also, Sudheimer et al. (2014) reported that high standards of IL- 6 and TNF- $\alpha$  were accompanied with low hippocampal volumes which indicates cognition decline with no such change for IL-8 [47].

Inconsistence, Baune et al. studied that poor performance of memory and speed was associated with high concentration of IL- 8 but not for IL-6 and TNF- $\alpha$  in elderly patients [48].

The aging process in human which was characterized by high, low grade pro-inflammatory cytokines was named as (inflamm-aging) in 2000 [49]. Recently, it is called as (Garb-aging) and it is referred to the accumulation of molecular endogenous macromolecules (molecular garbage) due to a defect in cell autophagy leading to activation of inflammasome in macrophages [50]. Several conditions such as DNA damage, ROS and telomerase loss leading to what's called as senescence-associated secretory phenotype (SASP) with increased scales of metalloproteinases, pro-inflammatory cytokines and growth factors promoting tissue and systemic inflammation [51]. The decrease in vitamin K level has been accompanied with increased aging and age related disorders by disturbing the gamma carboxylation process of VKDPs such as GRP and Gas6 included in pathological calcification and apoptosis and via modifying oxidative stress, inflammation and

mitochondrial dysfunction [52]. Also, aging has been associated with reduction in the mitochondrial activity regarding the respiratory chain function and the production of adenosine triphosphate (ATP) [53, 54]. Recent studies proposed that oxidative stress causing injury to the DNA present in the mitochondria creating dysfunction of the mitochondrial proteins leading to a state of chronic and systemic inflammation that alter most of the age related disorders [55, 56]. Furthermore, there were few studies considering the effect of vitamin K on the mitochondrial function; Vos M et al. (2012) stated that MK4 can play a role as an electron carrier in supporting and restoring the mitochondrial function [57].

On studying the anti-inflammatory effect of vitamin K, a previous study achieved on human fibroblasts treated with LPS endotoxins; stated that all types of vitamin K (K1, MK3, MK4 and MK7) could inhibit the LPS-induced expression of IL-6 with greater activity of MK-4 than phylloquinone [8]. Consistently, other clinical studies documented the inverse relationship between vitamin K and active CRP, IL-6 and intercellular adhesion molecule 1 (ICAM-1) [58]. Recently, the low level of serum phylloquinone was correlated to disability, morbidity, limitation and fragility in elderly [59, 60]. In addition, inflammation was found to accelerate aging in these people and further enhance the functional decline and disability [61]. Various studies characterized the relationship between inflammation and muscle weakness in elderly [62- 64]. A syndrome called sarcopenia was diagnosed in those people with increased loss of muscle mass and strength and increased levels of inflammatory cytokines such as IL-6, TNF- $\alpha$  and CRP [64, 65].

## **6.Conclusion:**

The present study highlights the role of vitamin K as an anti-inflammatory agent. Also, it provides an idea about the relationship between inflammation and aging. Although fewer studies estimate the benefit of vitamin K complements in elderly, the dietary intake of this vitamin can support the body defense mechanism against inflammation in those people.

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