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Vitamin K and The Immune System

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ABSTRACT

Vitamin K is a vitamin fat-soluble with the main function as an anticoagulant. The active form of vitamin K can be divided into two categories, namely vitamin K1 (phylloquinone) can be found in photosynthetic plants and vitamin K2 (menaquinone) comes from bacteria, a source in foods we can find this in fermented foods like natto or soybean product which fermented by *Bacillus natto*. This literature review was conducted through searching in databases like PubMed, and Elsevier using keywords like vitamin K, Immune system, and inflammation. The aim of this article is to present the mechanism of vitamin K related to the immune system. The role of vitamin K in physiological functions is well known worldwide, such as blood coagulation, bone metabolism, and regulation of several types of enzymes. Apart from this role, vitamin K also acts as a cofactor in several plasma proteins, so this vitamin can influence immune responses. Recent studies have found vitamin K links to inflammatory diseases. Vitamin K also induces an autophagy pathway. However, information regarding the role of vitamin K in the immune system is limited.

Introduction

Vitamin K is a fat-soluble vitamin. It is divided into two natural types, phylloquinone (K1) and menaquinone (K2) while the synthetic form is known as menadione (K3)[1,2]. Humans and animals cannot bio synthesize this vitamin, the primary source comes from plants that can photosynthesize[3]. Vitamin K1 can be found in green leafy vegetables such as spinach, broccoli, cabbage, and lettuce. Additionally, plant oil like canola oil, olive oil and soybean oil are a good source of phylloquinone. Vitamin K2 provided by fermented foods like natto and cheese[4].

Intestine is an organ that responsible to absorb vitamin K, transportation of vitamin K to the liver helped by triglycerides-rich lipoprotein chylomicrons, then activate K-dependent protein[5]. The absorption of vitamin K1 needs energy in the small intestine, while vitamins K2 and

K3 are absorbed by passive diffusion in the small intestine and colon. All the process absorption requires pancreatic fluid, bile salt, and a little fat[6].

The classical function of vitamin K is blood coagulation and bone metabolism[7], and vitamin K also the regulation of some enzyme systems[5,8]. The recent study about vitamin K focuses on the immune system, particularly T cells and inflammatory pathways. Studies reported that vitamin K influenced immune responses through redox-dependent manners and increased the number of regulatory T cells. Research on two vitamin K derivatives vitamin K3 and vitamin K5 showed the effect on suppression of cell proliferation and production of several cytokines activated by T cell mitogen[9]. The other vitamin K derivative, vitamin K2, can inhibit TNF-α, IL-1α, and IL-1β by dose dependently[10]. This study is a literature review that summarizes several journals related to the effects of vitamin K on the immune system.

Method

All the database collected from search engine PubMed and Elsevier on May 19th – 20th 2021 using keywords vitamin K, Immune system, and inflammation. The inclusion criteria are articles in English, the range time of journal published 2011-2021, free full text, study design is a clinical trial, the articles discuss about vitamin K or the derivates affects to immune system.

Results and Discussion

I. Vitamin K affects the immune system

The Immune system has a central function in the body's defense due to fighting pathogen such as virus, bacteria, parasite, and other organisms from an outside body, promoting protective immunity while maintaining tolerance to self[11]. The vitamin has a positive effect on the immune system, particularly on the innate immune system[12]. The essential of the innate system is the complement system that contains more than 30 proteins, it stimulates the adaptive immunity in three pathways namely classical, lectin and alternative pathways. Vitamin K is the main factor to the modification of protein S that is related to C4b-binding protein (C4BP), a potential inhibitor in lectin and classical pathways. C4BP induces proliferation and activation of B lymphocytes by binding with CD40. In conclusion, vitamin K affects immunity indirectly[13].

The research has been reported that factor Xa (FXa), one of the vitamin K-dependent complexes responsible for coagulation, regulates cytokine pro-inflammation production such as Tumor Necrosis Alpha (TNFα) and Interleukin-6 (IL-6) via proteolytic activation (PAR1 and PAR2) and stimulate TLR in myeloid cells[14]. Additionally, derivatives of vitamin K, vitamin K3 and vitamin K5, activate T cells and inhibit proliferative response and cytokine productions [9,15]. Hatanaka's study also showed a decrease of cytokine proinflammatory TNFα, IL-4, IL-6 and IL-10. Vitamin K derivatives also increase the frequency of CD4+, CD25+, and Foxp3+ Treg cells[9].

The others study about vitamin K reported by Yang *et.al* that menaquinone-7 (MK-7), a subtype of vitamin K2, inhibits ROS production and is effective to decrease IL-6, TNFα, CCL2, and CXCL10[16]. Menadione interacts with thiol antioxidant GSH (GSH is a reduced form of Glutathione) and suppresses extracellular signal-regulated kinase (ERK), c-Jun NH2-terminal kinase (JNK) and nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) expression can be suppressed[15,17].

II. Vitamin K related to autoimmune disease

The immune system protects the body from invading organisms such as bacteria, virus, and parasites, and maintains tolerance to self. Autoimmune disease occurs when the immune system attacks self-molecules due to autoreactive immune cells[11,18]

Table 1. Study of vitamin K-related autoimmune disease

Author, Year	Subjects (gender/Age)	Design Study	Findings
Nakajima, et.al.[19] 2011	47 people with CD (age 40±3.0) 40 people with UC (age 44±16) 41 people HVs (age 38±11)	Case-Control	Vitamins K and D are insufficient in patients with IBD. Insufficiency of vitamin K is suggested to be associated with inflammatory processes of CD.
Nowak, et. al,[20] 2014.	111 children (6-18 years old) IBD divided to: CD: 63 UC: 48	Cross-Sectional	Vitamin K deficiency was more common in patients with higher CD activity, in CD patients with higher mass Z-scores, and less in children with CD treated with infliximab.
Ekman, et.al,[21] 2011	96 patients SLE (85 women, 11 male) with 14 – 85 years old.	Cohort	The plasma concentrations of Gas6 and sAxl vary with disease activity in SLE, in particular GN, and may have a role in lupus pathogenesis.
Wu, et.al,[22] 2011	96 patient SLE (85 women, 11 male), patient RA 183 (68 men; 115 women).	Cohort	Patients with SLE have a strong correlation sMer levels and SLEDAI, but not in RA with the DAS.
Recarte et, all,[23] 2014	Plasma sample of 50 patients SLE and 50 healthy individuals. Mean age 40 years	Cross-Sectional	Plasma concentrations of GAS6 were higher and, total and free ProS were lower in the SLE patients compared to controls, even when patients on oral anticoagulant treatment were discarded
Meza, et, al.[24] 2019	130-woman SLE	Cross Sectional	Overweight in SLE patients is associated with increased clinical activity and deficiency of vitamin K and other nutrients.
Kaiser,[25] 2013	SLE	Cohort	Two genetic variants in VKORC1 associated to SLE development in Asians

IBD has 2 major types namely Crohn's Disease (CD) and Ulcerative Disease (UD). The previous study has found the link between low levels of vitamin K with CD. Although the mechanism of vitamin K effect on CD remained unclear[19]. In line with Nowak's study in pediatric IBD lack of vitamin K status higher on patient CD than UC. Patient CD who gets treatment infliximab has a good vitamin K status, hypothesized that patients with corticosteroid and infliximab have a better condition in IBD activity, so the patient can absorb the vitamin K intake. The other factor that affects on vitamin K is higher body mass, in pediatric IBD with higher mass Z-score have better vitamin K level than those who were vitamin K-sufficient[20].

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease categorized by abnormal regulation of the immune system. The effect of vitamin K on activity SLE has been studied. One of them is research from Ekman, et al., they said that the concentration of Growth Arrest Specific Gene-6 (GAS 6) and its receptor is linked to the activity SLE disease through the inflammation that happened and affect to Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, especially increased in patients with anti-DNA antibodies, leukopenia and glomerulonephritis (GN). Growth Arrest Specific Gene-6 (GAS6) and its receptor can be of biomarkers of SLE disease activity[21]. Wu,*et al.* confirmed the increase of sMer receptor in active SLE and increased the SLEDAI, sMer that important to phagocytosis for the apoptotic body[22]. In line with Ekman's study, research from Recarte, *et.al* said that higher values GAS6 and sMerTK in patients SLE with renal failure[23]. It seems like the GAS6 and its ligand are linked in renal disease.

The other study showed that body mass index is associated with the SLEDAI index score. SLE patients with excess weight (BMI > 25 kg/m^2) showed a higher score of clinical activity compared to SLE patients in normal BMI and SLE patients also lack consumption of some nutrients, including vitamin A, vitamin D, and vitamin E and vitamin K[24]. Vitamin K also effect indirectly genetic SLE in Asians through vitamin K epoxide reductase enzyme complex (VKOR) that encoded by VKORC1, the study compared genetics was conducted by Kaiser, *et.al* reported two genetic variants in VKORC1 (rs9934438 and rs9923231), involved in vitamin K reduction and associated with SLE development in Asians[25].

III. Vitamin K related to cancer

There are many of studies about vitamin K related to cancer, especially about antiproliferative effects of vitamin K on cancer cells[26,27]. Vitamin K2 block the G1 phase of cell cycle and induce caspase-3 that responsible to apoptosis. Cancer treatment focuses on mitochondria, due to mitochondria is associated with apoptosis to control cell numbers[28]. Vitamin K2 also induce mitochondrial-related apoptosis in bladder cancer[26].

According to the study in Japan, vitamin K2 induces the expression of Bak and Bax in HeLa cancer cells. Upregulation of Bak, Bax and Bcl-2 family proteins can lead to the loss of mitochondria

membrane directly and indirectly[29]. Vitamin K2 prevents the secondary form of tumors in the liver tissue and increases the survival rate in hepatocellular carcinoma patients. The mechanisms might involve inhibition of NFκB and the activation of apoptotic pathway[30].

Autophagy is a cytoprotective survival pathway, cells will remove dysfunctional components that are degraded by lysosomes. Autophagy plays a role in preventing cancer. Additionally, vitamin K inhibits cell growth via apoptosis and autophagy[27]. The randomized control trial study suggested a high green leafy vegetable diet where vitamin K can be found, and be consumed by adults at a higher risk of colon cancer to reduce the progressivity[31].

Conclusion

In conclusion, vitamin K has 2 forms, natural (K1 and K2) and synthetic form (K3). Green leafy is the main source of vitamin K. Vitamin K has many functions for the immune system such as regulation of cytokine pro-inflammation, inhibition of ROS, activation of the apoptotic pathway, and inhibition of NFκB.

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