



# Vitamin E and Autoimmune Diseases: A Narrative Review

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### ABSTRACT

Autoimmune diseases are characterized by the attack of the immune system to normal tissues. Patients with autoimmune diseases usually have the deficiency of dietary factors that may be related to the etiology of these conditions. Given the role of vitamin E as a physiologic stabilizer of lysosomal membranes, its deficiency can initiate the process of autoimmune diseases or accelerate its progress. It is supposed that vitamin E could reduce oxidative stress, which is an important factor in the pathogenesis of autoimmune diseases. The literature review is indicative of a decrease in the serum levels of vitamin E in almost all autoimmune diseases. Furthermore, there is evidence regarding the possible therapeutic value of vitamin E in the management of autoimmune diseases. Owing to the anti-inflammatory and protective effect of vitamin E against free radicals, and also its important effect on cytokines levels, this vitamin may play a powerful role in the prevention and treatment of rheumatoid arthritis, as well as joint inflammation and damage. Moreover, increased vitamin E intake might decrease the incidence and severity of certain autoimmune diseases through the regulation of the immune system.

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## Introduction

The effect of vitamin E on the immune system is reportedly related to its capability in the stimulation of the defense mechanism through antioxidant activity. The current literature is suggestive of a relationship between vitamin E deficiency and rheumatic diseases. Accordingly, there are several studies investigating rheumatologic conditions, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome, Behçet's disease, celiac disease, inflammatory bowel diseases (IBD), and systemic sclerosis (i.e., scleroderma), in this regard (1-6). In view of the mentioned studies, vitamin E was suggested as an extrinsic factor capable of affecting autoimmune diseases (7).

## Vitamin E

Vitamin E is synthesized only by plants and is

the general descriptor for tocopherols and tocotrienols (8,9). Naturally, there are eight forms of vitamin E, including the alpha, beta, gamma, and delta classes of tocopherol and tocotrienol, which are present in fat-containing foods (10).

Vitamin E plays an important role in antioxidant function and is critical for the prevention of polyunsaturated fatty acids oxidation in tissues (9). This vitamin acts as a powerful free radical scavenger, especially during the oxidation of fat and propagation of free radical reactions (10,11). Vitamin E is primarily located in the organelle membranes to protect the cell membranes from free radical attacks (10). Accordingly, alpha-tocopherols reduce the production of newly-formed free radicals. On the other hand, gamma-tocopherol neutralizes the already produced free radicals.

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## Vitamin E and immune system

In addition to having an antioxidant activity, vitamin E contributes to the function of the immune system. The main impact of vitamin E on the immune system is related to its capability in the stimulation of the defense mechanisms accomplished by the enhancement of humoral and cell immune responses, as well as phagocytic functions (10).

The role of vitamin E in the regulation of the immune system could be understood through its high concentration in lymphocytes and mononuclear cells (12). The high concentration of polyunsaturated fatty acids in the lymphocyte membranes usually leads to lipid peroxidation mediated by free radicals, and consequently loss of membrane fluidity (13,14). Low membrane fluidity decreases the exposure of membrane receptors, and finally their activities (13,14). Regarding this, it is not surprising that vitamin E has a profound effect on the immune system by antioxidant activity.

Studies suggest that vitamin E is associated with autoimmunity, as well as anti-inflammatory and immunomodulatory functions (15,16), especially in several inflammatory diseases (17). It has been suggested that vitamin E deficiency can lead to damages in the lysosomal membranes, thereby initiating the autoimmune process (7,18). Autoimmune diseases like scleroderma and SLE could be successfully controlled by vitamin E (7).

Studies about the effect of vitamin E on RA demonstrate that vitamin E may reduce the risk of developing this disease through its antioxidant effects (19-21). Furthermore, evidence on Behçet's disease is indicative of the useful effect of vitamin E on this condition (22,23). Celiac disease limits the sufficient absorption of fat-soluble vitamins, such as vitamins A, E, and K, through intestinal villi damage. This deficient fat-soluble vitamin absorption may be responsible for some of the neurologic symptoms reported by such patients (3,24). In addition, the local administration of vitamin E reduces the development of colon inflammation in patients with inflammatory bowel disease (25).

Based on this evidence and with regard to the association of oxidative stress with the pathogenesis of autoimmune diseases (22,23,26,27), it is necessary to consider the possible role of vitamin E in the prevention of oxidative stress in these diseases. With this background in mind, the present review study was conducted to review the current evidence regarding the impact of vitamin E deficiency on autoimmune disorders. This review also aimed to discuss the accumulating evidence pointing to the possible therapeutic effects

of vitamin E on autoimmune diseases.

## Literature review

To review the role of vitamin E in autoimmune diseases, we searched multiple databases, including PubMed, Science Direct, and Google Scholar. The searching process was performed using the following keywords: "Vitamin E", "Autoimmune diseases", "Rheumatoid arthritis", "Systemic lupus erythematosus (SLE)", "Sjögren's syndrome", "Behçet's disease", "Celiac disease", "Inflammatory bowel diseases", and "Systemic sclerosis (scleroderma)". The abstracts and full-texts of the articles related to the subject of interest and published in English language without time limitation were reviewed. After excluding the irrelevant articles, the remaining studies were reviewed meticulously.

## Vitamin E and Rheumatoid arthritis

The RA is a chronic disease that is usually treated with non-steroidal anti-inflammatory drugs and biological agents with antioxidant properties. According to the epidemiological studies, a diet with low antioxidants is associated with the increased risk of RA outbreak (28-30). Accordingly, it has been supposed that vitamins with antioxidant properties may effectively help in the management of RA.

Since vitamin E has anti-inflammatory and anti-analgesic properties, it may have a considerable impact on inflammatory diseases, like RA. In support of this notion, Haleagrahara et al. showed that an oral supplementation of  $\delta$ -tocotrienol potentially reduced the progression of joint destruction in the rat model of collagen-induced arthritis (31). Furthermore, some studies reported a correlation between the level of vitamin E and suppression of RA development (28,32,33).

In a primary study conducted in 1983, vitamin E-deficient diet group of rats demonstrated severe inflammatory reactions and low serum levels of lysosomal enzymes. On the other hand, in the vitamin E-supplemented diet group, the protective effect against free radical caused by lipid peroxidation led to leg swelling and depressed the albumin to globulin (A/G) ratio in rats (34). Xiong et al. reported that vitamin E could reduce the levels of cytokines in a murine model of RA (28).

Considering the anti-inflammatory and protective effects of vitamin E against free radicals and also the significant effect of this vitamin on cytokine levels, it may have a powerful role in the prevention and treatment of RA and the subsequent joint inflammation and damage. The analgesic effect of vitamin E in RA, which is independent of its anti-inflammatory properties, was shown in a

clinical trial.

In the mentioned study, the administration of  $\alpha$ -tocopherol (600 mg twice a day) for three months in comparison to placebo in 42 RA patients showed a significant decrease in the morning and evening pain of vitamin E group as assessed by visual analog scale (mean morning pain score decrease of  $-0.56$  in vitamin E group vs.  $+0.54$  in placebo group;  $P=0.006$ ). However, no significant difference was observed between the two groups regarding inflammatory disease activity measured by the Ritchie articular index and early morning stiffness (35).

### Vitamin E and Systemic Lupus Erythematosus

Systemic lupus erythematosus is a multisystemic chronic disease with an unknown etiology (36). Inflammatory process and high titers of several autoantibodies in SLE occur in response to dyslipoproteinemia and oxidative damage (36,37). In a study, vitamin E was introduced as an effective and nontoxic therapy for SLE (38). Additionally, the combination of fish oil and vitamin E reportedly resulted in the reduction of several SLE mediators, such as inflammatory cytokines, and higher antioxidant capacity in a mouse-SLE model (6,39).

In another study, researchers suggested vitamin E as an alternative treatment for SLE; however, they pointed out that vitamin E could regulate antibody titer and reduce autoantibody production via a mechanism independent of antioxidant activity (37). Evidence supports the effective impact of vitamin E on SLE. Nonetheless, except the aforementioned studies, there is no study investigating the actual mechanism of vitamin E in SLE patients and SLE therapy. Therefore, future studies are required to fully investigate the association between vitamin E and SLE.

### Vitamin E and Sjögren's syndrome

Sjögren's syndrome is a systemic autoimmune disease, which engages lymphocytic infiltrates in exocrine organs and accompanies with a decrease in salivary secretion (40). Szodoray et al. demonstrated the elevation of vitamin E level in primary Sjögren's syndrome patients, compared to healthy individuals. They also observed a positive correlation between the plasma levels of vitamin E and natural killer and type 1 T helper cells that could be a consequence of ongoing immunoregulatory abnormality in primary Sjögren's syndrome (41).

On the other hand, Aguglia et al. reported very low vitamin E concentrations in the serum of two brothers with Marinesco-Sjogren syndrome (1). This discrepancy may be related to the investigation of different forms of Sjögren syndrome in the mentioned studies.

It seems that mutation in SIL1 gene is responsible for chylomicron secretion, and subsequently very low serum levels of vitamin E in Marinesco-Sjogren syndrome. However, primary Sjögren's syndrome is a prototypic autoimmune disease with abnormality in B- and T-cell responses to autoantigens. Consequently, the difference in vitamin E levels could be related to the pathology of this form of Sjögren's syndrome. Patients with Sjögren's syndrome may benefit from the enhancement of vitamin E in their diet (42).

### Vitamin E and Behçet's disease

Behçet's disease is a rare systemic vasculitis disorder with an unknown etiology, which is manifested by multisystem symptoms, such as the recurrent attacks of oral aphthous ulcers, genital sores, skin lesions, and uveitis (43-45). Lipids peroxidation in the cell membranes and subsequent tissue injury are the results of decreased antioxidant defense mechanisms, mediated by free oxygen radicals (43).

In a study, patients with active Behçet's disease had significantly lower vitamin E levels, compared to controls. This indicates that increased oxidative stress products could reduce vitamin E levels in such patients. Accordingly, in the mentioned study, supplementation with vitamin E in patients with active Behçet's disease resulted in the active inhibition of the free radical production (43).

Other studies also suggest that vitamin E supplement may strengthen the antioxidant defense system and could be useful for Behçet's disease (4, 46). Furthermore, evidence reveals that vitamin E exerts a part of its radical inhibition by increasing vitamin A and beta-carotene concentrations (46). In summery, it can be concluded that vitamin E supplementation could help enhance vitamin E level in patients with Behçet's disease, thereby increasing the immune function through its antioxidant activity.

### Vitamin E and celiac disease

Celiac disease is a genetically-linked immune-mediated intolerance to gluten, which usually causes the malabsorption of micronutrients, such as iron, vitamin B12, vitamin D, and calcium (47,48). Since fat-soluble vitamins, like vitamins A, E, and K, are absorbable in the upper intestine, patients with celiac disease who have damaged intestinal villi may develop the deficiency of fat-soluble vitamins. Several studies suggested associations between vitamin E deficiency in celiac disease and occurrence of neurological complications (3,24). They also reported that vitamin E therapy can improve neurologic dysfunction in patients with vitamin E deficiency (3,24,49).

On the other hand, Ackerman et al. reported a case of celiac disease with vitamin E deficiency and neurological complications whose symptoms did not improve with vitamin E supplementation (50). Furthermore, some studies reported multiple cases of classic celiac disease with ataxic syndrome that showed normal vitamin E concentrations (51-54).

In general, it seems that vitamin E deficiency could be the cause of neurological complications in some individuals with celiac disease; however, it cannot be the case for all patients suffering from this disease. In support of this notion, researchers estimated that neurological manifestations occur in about 10% of the patients with celiac disease who have no vitamin E deficiency (24,55-57). Overall, the mentioned studies indicated that vitamin E supplementation could ameliorate neurologic dysfunction when it is responsible for neurologic degeneration.

#### **Vitamin E and inflammatory bowel diseases**

Inflammatory bowel diseases are inflammatory disorders with a chronic course, which mainly involve the alimentary tract, especially the colon and small intestine. These are associated with an imbalance of the intestinal microbiota (58,59). The IBDs are categorized as ulcerative colitis or Crohn's disease. They can affect any segment of the gastrointestinal tract from the mouth to the anus. Due to the gut mucosal inflammation and decreased oral intake, patients inflicted with such conditions are at a high risk for vitamin and mineral deficiencies (2). Several studies have mentioned vitamin E deficiency in patients with IBD. In addition, there is evidence revealing that this state of vitamin E deficiency adversely affects the course of disease (2,60-63).

Researchers suggest that the high antioxidant and anti-inflammatory activity of vitamin E could improve the lesions caused by ulcerative colitis (64,65). Additionally, Mirbagheri et al. showed that the local administration of vitamin E reduced the development of the colon inflammation (25). Vitamin E can also suppress the activation of nuclear factor- $\kappa$ B, thereby resolving the inflammation in the intestines (66,67).

Furthermore, a low concentration of antioxidant molecules (e.g., glutathione and superoxide dismutase) in colitis patients could restore after treatment with vitamin E (64). On the other hand, vitamin E therapy is reported to eliminate cytokine production, a major contributor to the colon inflammation (64). In summary, the literature emphasizes that vitamin E has a great potential to reverse ulcerative colitis.

#### **Vitamin E and systemic sclerosis**

Systemic sclerosis (i.e., scleroderma), a connective tissue disease, is characterized by the progressive thickening of the skin and fibrosis of internal organs, microvasculature damage, and autoimmunity (68). The role of oxidative stress in the pathogenesis of this disease has been indicated in the literature. First, Murrell et al. suggested that an abnormal generation of reactive oxygen species (ROS) and a reduction of antioxidants could explain most of the pathologic features in scleroderma patients (69).

Researchers found an association between free radicals, oxidative stress, and scleroderma through observing reduced serum levels of some antioxidants, like ascorbic acid (70),  $\alpha$ -tocopherol (vitamin E) (5), carotene, and peroxiredoxin I (71). Balbir-Gurman et al. also demonstrated that scleroderma is associated with high rates of lipid peroxidation and low levels of antioxidant enzymes (72). In another study, Sambo et al. showed that ROS generation induced the expression of type I collagen gene in scleroderma fibroblasts that can lead to the accumulation of collagens in the affected organs (73).

On the other hand, oxidative stress has a substantial role in the generation of autoantibodies, suggested to be involved in scleroderma, and exhibition of Th2 cytokine profile (74). Moreover, ROS is suggested to increase transforming growth factor beta (TGF- $\beta$ ) release. This factor acts as a potent activating stimulus of H<sub>2</sub>O<sub>2</sub>-generating NADH oxidase. In addition, TGF- $\beta$  is the suppressor of antioxidant enzymes in fibrotic conditions, such as scleroderma (74).

The current evidence indicates that free radical accumulation is a major factor that characterizes scleroderma lesions. In regard to this notion, some studies focused on the special role of antioxidant agents in the suppression of ROS generation in an attempt to find new therapeutic modalities for the management of scleroderma. Antioxidants, such as vitamin E, could alter transcription factors, as well as signal transduction pathways (75). Therefore, they may be beneficial in scleroderma therapy.

Scleroderma patients are reported to have reduced levels of  $\alpha$ -tocopherol (vitamin E) (5). In an attempt to heal lesions in scleroderma, vitamin E supplementation resulted in the improvement of the dermatologic manifestations of this condition (76). Ayres et al. reported a successfully treated patient who received 800 IU oral vitamin E daily and vitamin E gel (50 IU per mL twice a day) for ulcerated fingers.

Fiori et al. suggested that vitamin E increases cytosolic phospholipase A2 and cyclooxygenase

expression. This, in turn, leads to prostacyclin release with a considerable vasodilatory effect, inhibition of platelet aggregation, growth and stabilization of the granulation tissue, and reepithelization. They also showed that the application of vitamin E reduces the time of healing and could be a good choice for the management of ulcers in scleroderma (77).

Moreover, Sambo et al. suggested that  $\alpha$ -tocopherol could inhibit fibroblast proliferation. They noted that this inhibition is mainly achieved via the inhibition of protein kinase C (42). Regardless of the nature of vitamin E efficacy in fibroblast proliferation, several studies indicated the beneficial effect of this vitamin in the treatment of dermatological diseases and ulcers in scleroderma (77-79).

Experimental evidence suggests that both topical and oral vitamin E have therapeutic effects on ulcers. Furthermore, antioxidant, photoprotective, and skin barrier-stabilizing properties of this vitamin prevent the creation of new cutaneous lesions in scleroderma.

## Conclusion

Almost all the reviewed articles in the existing literature showed an association between the serum levels of vitamin E and autoimmune diseases. According to the results of the reviewed studies, autoimmune diseases, like scleroderma and SLE, could be successfully controlled by vitamin E administration. Nevertheless, the current available data about such autoimmune diseases do not specify whether vitamin E deficiency is the cause of the disease or its consequence. Therefore, further studies are required to address the mechanisms by which vitamin E status affects autoimmunity in each autoimmune disease. In addition, it is essential to conduct large epidemiological studies in this regard.

Nonetheless, the evidence presented here indicated the beneficial effects of vitamin E administration on autoimmune diseases, especially the amelioration of inflammatory reactions. Furthermore, given the fact that vitamin E is responsible for preventing against lipid peroxidation, which contributes to the etiology of autoimmune diseases, dietary intake of vitamin E could be used as an important factor for the management of autoimmune diseases and their progress.

## Conflict of Interest

The authors declare no conflict of interest.

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