**Vitamin E and autoimmune diseases: a narrative review**


## Abstract

Autoimmune diseases are characterized by attack of the body's defense system to normal tissues. Patients with autoimmune diseases usually have deficiency of dietary factors that may be related to the etiology of these conditions. Since vitamin E is a physiologic stabilizer of lysosomal membranes, its deficiency can initiate the process of autoimmune diseases and may speed up 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 shows a decrease in serum levels of vitamin E in almost all autoimmune diseases. Also, the possible therapeutic value of vitamin E in the management of autoimmune diseases **is** pointed out. Owing to the anti-inflammatory and protective effect of vitamin E against free radicals and also the important effect on cytokines levels, it may have a powerful role in preventing and treatment of rheumatoid arthritis and also joint inflammation and damage. Increased vitamin E intake might decrease the incidence and severity of certain autoimmune diseases through regulation of the immune system.



**Keywords:** Vitamin E; tocopherols; tocotrienols; autoimmune diseases




## Introduction

The evidence shows that the effect of vitamin E on the immune system is related to its capability in stimulation of the body’s defense through antioxidant activity. The current literature demonstrates a relationship between deficiency of vitamin E and rheumatic diseases. The rheumatologic conditions studied in this regard include rheumatoid arthritis

(RA), systemic lupus erythematosus (SLE), Sjögren syndrome, Behçet's disease, celiac disease, inflammatory bowel diseases, and systemic sclerosis (scleroderma) (1-6).

In view of the mentioned studies, it has been suggested that vitamin E is 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 the antioxidant function and is critical for prevention of PUFA (polyunsaturated fatty acids) oxidation in tissues (9). This vitamin acts as a powerful free-radical-scavenger, especially during oxidation of fat and reactions that propagate free radicals (10, 11). It is primarily located in organelle membranes, where it protects the cell membranes from free radical attacks (10). In this way, alpha-tocopherols reduce production of newly-formed free radicals. On the other hand, gamma-tocopherol neutralizes the already produced free radicals.

***Vitamin E and the immune system***

Beside antioxidant activity, vitamin E contributes to the function of immune system. The main impact of vitamin E on the immune system is related to its capability in stimulation of the body's defenses by enhancing humoral and cell immune responses as well as phagocytic functions (10).

The role of vitamin E in regulation of the immune system could be understood through high concentration of vitamin E in lymphocytes and mononuclear cells (12).

High concentration of polyunsaturated fatty acids in lymphocyte membranes usually lead to lipid peroxidation mediated by free radicals and consequently loss of membrane fluidity (13, 14). Low membrane fluidity decreases exposure of membrane receptors and finally their activities (13, 14), therefore it is not surprising that vitamin E has a profound effect on the immune system by antioxidant activity.

Studies suggest that vitamin E is linked with autoimmunity, anti-inflammatory and immunomodulatory functions (15, 16), especially in several inflammatory diseases (17).

It has been suggested that deficiency of vitamin E is related to damages in lysosomal membranes, thus 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 show that vitamin E may reduce the risk of developing RA through its antioxidant effects (19-21). Data presented in studies about Behçet's disease shows useful effect of vitamin E in this condition (22, 23). Because of intestinal villi damage in celiac disease, absorption of fat-soluble vitamins like vitamins A, E and K is not enough. Thus, this deficient fat-soluble vitamin absorption may be responsible for some of the neurologic symptoms reported by such patients (3, 24). Local administration of vitamin E also reduces the development of colon inflammation in patients with inflammatory bowel disease (25).

Based on this evidence and with regard to the association between oxidative stress and pathogenesis of autoimmune diseases (22, 23, 26, 27), the possible role of vitamin E in preventing oxidative stress in these diseases should be considered. Thus, in this review article, we intended to review the current evidence regarding the impact of vitamin E deficiency in autoimmune disorders. This review also discusses the accumulating evidence pointing to possible therapeutic effects of vitamin E in 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 using the following keywords: vitamin E, autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren syndrome, Behçet's disease, celiac disease, inflammatory bowel diseases and systemic sclerosis (scleroderma).

We reviewed all abstracts and full-texts of articles published in English language without time limitation. After excluding irrelevant articles, the remaining articles were reviewed meticulously.

## Discussion

*Vitamin E and Rheumatoid arthritis*

RA is a chronic disease that is usually treated with non-steroidal anti-inflammatory drugs (NSAIDs) and biological agents with antioxidant properties. Epidemiological studies have shown that a diet with low antioxidants is associated with increased risk of RA outbreak (28-30). Thus, it has been supposed that vitamins with antioxidant properties may help to manage RA effectively.

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 δ-tocotrienol potently reduces the progression of joint destruction in the rat model of collagen-induced arthritis (31). Also, some studies have revealed a correlation between the level of vitamin E and suppressing development of RA (28, 32, 33).

A primary study in 1983 showed severe inflammatory reactions and low serum levels of lysosomal enzymes in vitamin E-deficient diet group in rats (34). While in the vitamin E-

supplemented diet group, 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. showed that vitamin E can reduce the levels of cytokines in a murine model of RA (28).

Taken together, because of the anti-inflammatory and protective effects of vitamin E against free radicals and also the important effect on cytokines levels, it may have a powerful role in preventing and treatment of RA and subsequent joint inflammation and damage. The analgesic effect of vitamin E in RA has been shown in a clinical trial which this effect was independent of anti-inflammatory properties of vitamin E (35). Administration of α-tocopheral (600 mg twice daily) for three months in comparison to placebo in 42 RA patients showed a significant decrease in morning and evening pain assessed by visual analog scale in vitamin E group (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 existed between the two groups regarding inflammatory disease activity quantified by the Ritchie articular index (RAI) and early morning stiffness (35).

***Vitamin E and Systemic Lupus Erythematosus (SLE)***

SLE is a multisystemic chronic disease with unknown etiology (36). Inflammatory process and high titers of several autoantibodies in SLE occur in response of dyslipoproteinemia and oxidative damage (36, 37).

A previous study reported that vitamin E could be an effective and nontoxic therapy for SLE (38). Additionally, the combination of fish oil and vitamin E showed a reduction in several SLE mediators such as inflammatory cytokines and higher antioxidant capacity in a mouse-SLE model (6, 39).

In another study, researchers suggested that vitamin E can be an alternative treatment for SLE, but they pointed out that vitamin E could regulate antibody titer and reduce

autoantibody production via a mechanism independent of antioxidant activity (37). Studies support effective impact of vitamin E on SLE but except mentioned studies, there is no study that analyzes the actual mechanism of vitamin E in SLE patients and SLE therapy. Accordingly, future research studies are required to fully investigate the association between vitamin E and SLE in details.

***Vitamin E and Sjögren syndrome***

Sjögren syndrome (SS) is a systemic autoimmune disease which engages lymphocytic infiltrates in exocrine organs and a decrease in salivary secretion (40).

Szodoray et al. showed the increase of vitamin E level in primary Sjögren syndrome compared to healthy individuals (41). Also, a positive correlation was reported between plasma levels of vitamin E and natural killer (NK), and type 1 T helper (Th1) cells that could be a consequence of ongoing immunoregulatory abnormality in primary Sjögren syndrome (41). In contrast, Aguglia et al. reported Marinesco-Sjogren syndrome in 2 brothers with very low vitamin E concentrations in serum (1). These contradictory findings may be related to the different forms of Sjögren syndrome in the mentioned studies. It seems that mutation in the SIL1 gene is responsible for chylomicron secretion and subsequently very low serum levels of vitamin E in Marinesco-Sjogren syndrome. But, primary Sjögren syndrome is a prototypic autoimmune with abnormality in B- and T-cell responses to autoantigens. Thus, difference in vitamin E levels could be related to pathology of this form of Sjögren syndrome. Patients with Sjögren's syndrome may benefit from increase of vitamin E in their diet (42).

***Vitamin E and Behçet's disease***

Behçet's disease is a rare systemic vasculitis disorder with unknown etiology which is manifested by multisystem symptoms such as recurrent attacks of oral aphthous ulcers, genital sores, skin lesions, and uveitis (43-45).

Lipids peroxidation in cell membranes and subsequent tissue injury are results of decreased antioxidant defense mechanisms, which is mediated by free oxygen radicals (43).

It has been demonstrated that vitamin E levels in active Behçet's disease BD were significantly lower when compared to controls, supporting that increased oxidative stress products could reduce vitamin E levels in such patients (43). Interestingly, in a previous study involving patients with active Behçet's disease, it was found that supplementation with vitamin E actively inhibited production of free radicals 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, findings showed 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 to increase vitamin E level in Behçet's disease and subsequently enhancement of the immune function by its antioxidant activity.

***Vitamin E and celiac disease***

Celiac disease is a genetically-linked immune-mediated intolerance to gluten which usually causes malabsorption of micronutrients such as iron, vitamin $B_{12}$, 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 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 patient 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).All in all, it seems that vitamin E deficiency could be the cause of the neurological complications in some individuals with celiac disease, but not all of them. In support of this notion, researchers estimated that neurological manifestations occur in about 10% of patients of celiac disease without vitamin E deficiency (24, 55-57). Overall, the mentioned studies indicate that vitamin E supplementation could ameliorate neurologic dysfunction when vitamin E is responsible of neurologic degeneration.

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

Inflammatory bowel diseases (IBD) 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). IBDs are categorized as ulcerative colitis or Crohn's disease. These can affect any segment of the gastrointestinal tract from the mouth to the anus. Due to gut mucosal inflammation and decreased oral intake, patients are at a high risk for vitamin and mineral deficiencies (2). Several studies have mentioned vitamin E deficiency in patients with IBD. Plus, there is evidence that this state of vitamin E deficiency adversely affects the course of disease (2, 60-63).

Researchers suggest that high antioxidant and anti-inflammatory activity of vitamin E could improve lesions after injury from ulcerative colitis (64, 65). Additionally, Mirbagheri et al.

showed that local administration of vitamin E reduced the development of colon inflammation (25). Vitamin E can also suppress transcription factor NF-κB activation. Via this, vitamin E can resolve inflammation in the intestines (66, 67). Furthermore, low concentration of antioxidant molecules (glutathione (GSH) and superoxide dismutase (SOD)) in colitis patients could be restore after treatment with vitamin E (64). On the other hand, vitamin E therapy eliminated 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 (scleroderma), a connective tissue disease, is characterized by progressive thickening of skin and fibrosis of internal organs, microvasculature damage, and autoimmunity (68). Studies showed the role of oxidative stress in the pathogenesis of this disease. First, Murrell et al. suggested that abnormal generation of reactive oxygen species (ROS) and a reduction of antioxidants could explain most pathologic features in scleroderma patients (69). Researchers found a link between free radicals, oxidative stress, and scleroderma through showing reduced serum levels of some antioxidants like ascorbic acid (70), α-tocopherol (vitamin E) (5) , carotene and peroxiredoxin I (71). Balbir-Gurman et al. also showed 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 finally exhibition of Th2 cytokine profile (74). Moreover, ROS were suggested to activate demonstrated to increase transforming growth factor beta (TGF-β)

release. This factor acts as a potent activating stimulus of $H_2O_2$-generating NADH oxidase. In addition, TGF-β is the suppressor of antioxidant enzymes in fibrotic conditions such as scleroderma (74).

Collectively, 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 suppression of ROS generation in an attempt to find new therapeutic modalities for management of scleroderma. Antioxidants such as vitamin E could alter transcription factors as well as signal transduction pathways (75). Therefore, this may be beneficial in scleroderma therapy. Reduced levels of α-tocopherol (vitamin E) in scleroderma patients have been reported (5). In an attempt for healing lesions in scleroderma, vitamin E supplementation has resulted in improvement of 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 daily) 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 considerable vasodilatory effect, and inhibition of platelet aggregation and finally the growth and stabilization of the granulation tissue, as well as reepithelization (77). They also showed that application of vitamin E reduces time of healing and could be a good choice in the management of ulcers in scleroderma (77).

Moreover, Sambo et al. suggested that α-tocopherol could inhibit fibroblast proliferation. They noted that this inhibition is mainly achieved via inhibition of protein kinase C (42). Regardless of nature of vitamin E efficacy on fibroblast proliferation, several studies showed 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. Furtheremore, antioxidant, photoprotective, and skin barrier stabilizing properties of this vitamin prevent creation of new cutaneous lesions in scleroderma.

## Conclusion

Almost all the reviewed articles in the existing literature show an association between serum levels of vitamin E and autoimmune diseases. 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 that vitamin E deficiency is the cause of disease or may be a consequence of the disease. Therefore, further studies addressing the mechanisms by which vitamin E status affects autoimmunity in each autoimmune disease as well as large epidemiological studies are required. Nonetheless, the evidence presented here shows beneficial effects of vitamin E administration on autoimmune diseases, especially amelioration of inflammatory reactions. . Furthermore, given the fact that vitamin E is responsible of preventing against lipid peroxidation which contributes to the etiology of autoimmune diseases, dietary intake of vitamin E could be used as important factor in managing of autoimmune diseases and their progress.

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