REVIEW

Ozden Canbay Gokcek[1]
Mehmet Ozkeskin[1]
Miray Baser[1]

[1] Ege University, Health Science Faculty, Department of Physiotherapy and Rehabilitation, İzmir, Türkiye

Corresponding Author:
Ozden Gokcek
mail: ozdencanbay@hotmail.com

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konuralptipdergi@duzce.edu.tr
konuralptipdergisi@gmail.com
www.konuralptipdergi.duzce.edu.tr

The Beneficial Effect of Exercise and Vitamin D Supplementation on Comorbidities Associated with Systemic Lupus Erythematosus

ABSTRACT

Objective: Systemic lupus erythematosus (SLE) is a multisystem chronic autoimmune disease characterized by recurrent and relapsing attacks that may affect the locomotor system as well as the liver and kidneys. Vitamin D deficiency is thought to play a role in the pathogenesis of SLE. Therefore, the primary aim of this literature review is to determine the role of vitamin D deficiency on SLE symptoms. The secondary aim is to explain the benefits of exercise on SLE-related comorbidities.

Methods: A comprehensive literature search on SLE symptoms, biochemistry, and pathophysiology was conducted via Google Scholar. The impact of exercise on comorbidities associated with SLE was examined.

Results: The precise etiology of the disease remains elusive, although there is mounting evidence that vitamin D deficiency is associated with symptoms of SLE. In addition to pharmacological treatment for the involvement of the locomotor system in SLE patients, physiotherapy applications are also included. This review presents evidence of the positive effects of exercise on pain, fatigue, and sleep problems caused by disease-related or side effects of pharmacological applications used in the treatment of SLE patients.

Conclusions: It is not possible to correct the symptoms of SLE associated with vitamin D deficiency by means of vitamin D supplementation alone. At this juncture, it is hypothesized that exercise may offer potential benefits in correcting vitamin D deficiency. Consequently, exercise exerts a beneficial influence on the comorbidities associated with SLE. Future studies should be planned to establish an appropriate exercise prescription for SLE.

Keywords: Systemic Lupus Erythematosus, Exercise, Fatigue, Pain, Sleep Disorders, Vitamin D

Egzersiz ve D Vitamini Desteğinin Sistemik Lupus Eritematozus ile İlişkili Komorbiditeler Üzerindeki Faydalı Etkisi

ÖZET

Amaç: Sistemik lupus eritematozus (SLE), lokomotor sistemin yanı sıra karaciğer ve böbrekleri de etkileyebilen, tekrarlayan ve nükseden ataklarla karakterize multisistem kronik otoimmün bir hastalıktır. D vitamini eksikliğinin SLE patogenezinde rol oynadığı düşünülmektedir. Bu nedenle, bu literatür taramasının birincil amacı D vitamini eksikliğinin SLE semptomları üzerindeki rolünü belirlemektir. İkincil amaç ise egzersizin SLE ile ilişkili komorbiditeler üzerindeki faydalarını açıklamaktır.

Yöntem: Google Akademik aracılığıyla SLE semptomları, biyokimyası ve patofizyolojisi hakkında kapsamlı bir literatür taraması yapılmıştır. Egzersizin SLE ile ilişkili komorbiditeler üzerindeki etkisi incelenmiştir.

Bulgular: D vitamini eksikliğinin SLE semptomlarıyla ilişkili olduğuna dair kanıtlar artmakla birlikte, hastalığın kesin etiyolojisi halen tam olarak bilinmemektedir. SLE hastalarında lokomotor sistem tutulumuna yönelik farmakolojik tedavinin yanı sıra fizyoterapi uygulamaları da yer almaktadır. Bu derlemede, SLE hastalarının tedavisinde kullanılan farmakolojik uygulamaların yan etkileri veya hastalığa bağlı olarak ortaya çıkan ağrı, yorgunluk ve uyku sorunları üzerinde egzersizin olumlu etkilerine dair kanıtlar sunulmaktadır.

Sonuç: D vitamini eksikliği ile ilişkili SLE semptomlarını sadece D vitamini takviyesi ile düzeltmek mümkün değildir. Bu noktada, egzersizin D vitamini eksikliğini düzeltmede potansiyel faydalar sağlayabileceği varsayılmaktadır. Sonuç olarak, egzersiz SLE ile ilişkili komorbiditeler üzerinde faydalı bir etkiye sahiptir. SLE için uygun bir egzersiz reçetesi oluşturmak üzere gelecekteki çalışmalar planlanmalıdır.

Anahtar Kelimeler: Sistemik Lupus Eritematozus, Egzersiz, Yorgunluk, Ağrı, Uyku Bozuklukları, D Vitamini.

INTRODUCTION

Background

Systemic Lupus Erythematosus (SLE), an autoimmune disease, is characterized by chronic inflammation and multiple organ damage due to the continuous production of autoantibodies (1). As immune cells are stimulated more frequently in SLE, autoantibodies and immunological complexes are produced. Additionally, cytokines including IL-17 and IL-10, chemokines, vasoactive peptides, oxidants, and proteolytic enzymes are released. In response to inflammatory cytokines, the liver secretes hepcidin, which inhibits the release of iron from macrophages and the absorption of iron from the gut, thereby preventing erythropoiesis (2). The accumulation of chronic oxidation products causes chronic inflammation, and irreversible tissue damage to the kidneys, lungs, and other tissues (3).

The cause of the disease is not fully known. Genetic predisposition, gender, and environmental factors are thought to trigger an abnormal immune response leading to the development of systemic lupus erythematosus (4). In addition, vitamin D deficiency is thought to play a role in the pathogenesis of SLE. It has been emphasized that 25-hydroxyvitamin D levels are low in various autoimmune diseases, including rheumatic diseases (5).

Therefore, our primary aim in this literature review is to determine the role of vitamin D deficiency on SLE symptoms. Our secondary aim is to explain the benefits of exercise on SLE-related comorbidities.

Main Text

Vitamin D and Deficiency in SLE: Vitamin D is a pro-hormone that can be consumed by food or produced in the skin's epidermis following exposure to UV rays. It has significant influence on the cardiovascular system, mineral metabolism, and bone health (6, 7). The result of a meta-analysis showed that SLE patients generally exhibited significantly lower serum vitamin D levels compared with healthy controls (7). In vitamin D deficiency, it has been found that there is a deterioration in the cell's ability to respond to pathological and physiological signals (8).

There is an opinion that the decrease in sleep duration and deterioration of sleep quality in SLE patients may be associated with low vitamin D levels (9). In addition, disease duration, anxiety, depression, subjective sleep quality, and sleep disturbances were found to be significantly associated with fatigue (10).

It has been reported that arthritis is improved with vitamin D supplementation in animal models of SLE (11), and disease activity and fatigue symptoms are improved in human models (12). However, the available literature is conflicting regarding the efficacy of vitamin D supplementation on symptoms and recovery in SLE (13-15).

Therefore, it is important to implement therapies aimed at improving the pathogenic mechanism causing vitamin D deficiency. Improving the function of the kidneys and liver, the source of metabolic transformations of vitamin D may have an important role in correcting vitamin D deficiency and alleviating the accompanying symptoms.

Vitamin D and Exercise: Vitamin D deficiency causes muscle pain and muscle weakness due to atrophy of type 2 muscle fibers, hypotonia, peak muscle contraction time, and prolongation of muscle relaxation time (16, 17). It has been observed that vitamin D receptors (VDRs) identified in muscle tissue are increased with vitamin D supplementation (18).

Vitamin D is lipophilic and tends to accumulate in adipose tissue. Vitamin D3 and 25(OH)D accumulation was observed in adipose tissue (19, 20). Exercise, an effective stimulus for lipid mobilization, helps mobilize vitamin D accumulated in adipose tissue (21, 22).

Particularly submaximal endurance training has been shown in the literature to significantly boost fat metabolism (23). Stored vitamin D metabolites are released when lipolytic enzymes release triglycerides from adipocytes. A number of substances, including insulin, beta-adrenergic hormones, atrial natriuretic peptides (ANPs), and brain natriuretic peptides (BNPs), influence lipolysis (24). The release of these hormones, the promotion of lipolytic actions, and the release of vitamin D metabolites from adipose tissue are all possible benefits of endurance exercise (25).

Sleep Problems and the Effect of Exercise in Systemic Lupus Erythematosus: Drugs that are commonly prescribed for the treatment of symptoms of rheumatic diseases and commonly used in SLE (Prednisone) may have adverse effects on sleep (26).

It has been shown in previous studies that vitamin D deficiency, which is very common in SLE patients, affects sleep quality, psychological state, and depression, including in the non-SLE population (27, 28). There is evidence that musculoskeletal pain caused by vitamin D deficiency also affects sleep quality (28). In addition, due to the immune regulatory role of vitamin D, an increase in the production of inflammatory cytokines, which can affect sleep patterns and quality, has been observed in deficiency. This can cause obstructive sleep apnea, airway myopathy, and chronic rhinitis in individuals (29).

Physical activity is considered a non-pharmacological complementary method recommended for treating sleep problems by improving sleep quality (30). In the literature, it is stated that exercise contributes positively to overall sleep quality (31). In a meta-analysis conducted in 2019, it was reported that exercise in the evening contributes to sleep positively (32).

In addition to improving the overall sleep quality of exercise alone, it can be effective for the treatment of sleep disorders due to vitamin D deficiency in SLE by providing vitamin D mobilization, which accumulates in adipose tissue.

Pain and The Effect of Exercise in Systemic Lupus Erythematosus: Lupus nephritis is one of the indicators of poor prognosis in systemic lupus erythematosus. According to the findings of an analysis in the literature comparing children with juvenile idiopathic arthritis (JIA) with active and inactive lupus nephritis and healthy controls, urinary Prostaglandin D synthase (PGDS) levels were reported to be higher in children with active lupus nephritis (LN) than in healthy controls and children with inactive lupus (33). This highlights that the increase in prostaglandins in SLE adversely affects the prognosis. Prostaglandins are mediators synthesized in the cells of the organism, involved in inflammation and pain formation. Vitamin D is involved in inhibiting the synthesis of Prostaglandin E2 (PGE2) in fibroblasts (34). Current studies have shown that vitamin D supplementation reduces musculoskeletal pain and levels of inflammatory cytokines, including prostaglandin E2 (PGE2) (35). In line with this information, the mechanism of action of vitamin D on pain is explained by the reduction of inflammation and the inhibition of PGE2, which affects pain formation.

In addition, exercise increases the secretion of endorphins and serotonin in the body (36). β-endorphins, which are part of the endogenous opioid system, are involved in pain relief. For this reason, by stimulating the body to secrete more endorphins with regular exercise, it is possible to benefit more from the analgesic effect of endorphins.

In a recent review including only RCTs, exercise and psychological interventions have been shown to improve pain, fatigue, depression, and quality of life in individuals with SLE (37). In addition, a recent pilot RCT reported improvement in hand function, pain, activity limitation, and quality of life with upper extremity resistance training in patients with SLE without a negative effect on disease activity (38).

Fatigue and The Effect of Exercise in Systemic Lupus Erythematosus: One of the most common symptoms in patients with SLE is fatigue. Several mechanisms have been described for how vitamin D deficiency can cause fatigue. Reduced exercise capacity (39), decreased strength (40), decreased quality of life (41), and elevated levels of weariness (42) are a few of the processes discovered in people with SLE. Fatigue may result from proximal muscular weakness brought on by a loss in type 2 muscle fibers due to vitamin D insufficiency (43).

In a study in the literature, individuals with chronic fatigue syndrome and controls without chronic fatigue syndrome were compared. Individuals with chronic fatigue have been found to have higher serum TNF-α levels (44). This indicates that TNF-α is elevated in the presence of sleep disorders and chronic fatigue. In a prospective cohort study of SLE patients, elevated serum TNF-α levels were seen (45). In addition, in another study conducted with lupus patients, a significant inverse correlation was found between serum 25(OH)D and TNF-α levels in patients (46). Starkie et al. reported that endurance exercise with 8 healthy male individuals significantly reduced TNF-α production (47).

Balsamo et al. evaluated a total of 50 individuals, including 25 premenopausal SLE patients with low SLE disease activity index and 25 healthy controls. They reported that muscle strength in SLE patients was lower than in the healthy control group. They provided evidence that insufficient muscle strength causes increased fatigue, decreased performance, and quality of life in SLE patients (48).

In the literature, aerobic exercise is widely recommended for individuals with SLE to increase exercise tolerance by increasing cardiovascular fitness. A meta-analysis of studies in individuals with SLE showed a significant increase and improvement in physical fitness and function of the exercise group compared to controls (49). Another study comparing 93 patients with SLE and 41 sedentary controls showed that patients with SLE had lower exercise capacity and muscle strength than sedentary controls, and reported more fatigue than sedentary individuals (40).

In an RCT conducted with children aged 7-15 years with SLE, it was emphasized that 12-week, twice-weekly supervised, moderate-intensity aerobic exercise is a safe and effective method to improve cardiorespiratory capacity (50).

The increase in cardiorespiratory capacity prevents the development of fatigue in individuals and provides an increase in physical functions and quality of life. In this respect, the exercises deemed appropriate by the physiotherapist for SLE patients contribute positively to the quality of life by providing improvement/decrease in the symptoms of the patient.

The Table 1 below provides a summary of the potential mechanisms by which vitamin D deficiency may affect sleep problems, pain, and fatigue in SLE. Furthermore, the table provides an overview of the potential benefits of exercise in this context.

Table 1. The effect of vitamin D deficiency and exercise on comorbidities in SLE.

Comorbidities in SLE	The Effect of Vitamin D Deficiency	The Effect of Exercise
Sleep Problems	Musculoskeletal pain caused by vitamin D deficiency affects sleep quality (28). Due to the immunoregulatory role of vitamin D, an increase in the production of inflammatory cytokines that may affect sleep patterns and quality is observed in vitamin D deficiency.	It is a non-pharmacological method recommended for the treatment of sleep problems (30). It contributes positively to general sleep quality (31). Especially exercise performed in the evening positively affects the transition to sleep (32). It may be effective in treating vitamin D deficiency-related sleep disorders in SLE by mobilizing vitamin D accumulated in adipose tissue (21, 22).
Pain	The mechanism of action of vitamin D on pain is explained by the reduction of inflammation and inhibition of prostaglandin E2, which affects pain formation (34, 35).	Exercise and psychological interventions reduce pain in individuals with SLE (37). Upper extremity resistance exercises reduce pain (38).
Fatigue	Fatigue may result from proximal muscle weakness caused by the loss of type 2 muscle fibres due to vitamin D deficiency (43). TNF-α is increased in the presence of sleep disorders and chronic fatigue. High serum TNF-α levels have been observed in patients with SLE (45). There is a significant inverse correlation between serum 25(OH)D and TNF-α levels (46).	Exercise improves physical fitness and functions (49). Patients with SLE have lower exercise capacity and muscle strength compared to sedentary controls. They report more fatigue than sedentary individuals (40). Supervised, moderate-intensity aerobic exercise twice a week for 12 weeks is a safe and effective method to improve cardiorespiratory capacity in SLE (50). Endurance exercises reduce fatigue by decreasing TNF-α production (47).

CONCLUSION

Prescription of exercises deemed appropriate for SLE patients by the physiotherapist may help to improve/reduce fatigue, sleep problems, and pain symptoms seen in SLE, improve the quality of life of patients, and eliminate vitamin D deficiency due to SLE. In this direction, the importance of physiotherapy applications should be emphasized in addition to medical treatment in SLE patients. Future studies should be planned to create an appropriate exercise prescription for SLE.

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