



The Relationship Between Serum Vitamin D Level and Systemic Lupus Erythematosus Activity

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Abstract

Background and aims: Systemic lupus erythematosus (SLE) is an autoimmune disease which involves various organs. Vitamin D is an essential ingredient in regulating the immune system. This study aimed to investigate the relationship between vitamin D and the severity of lupus activity.

Materials and Methods: This case-control study was carried out on 38 patients with lupus on the basis of the American College of Rheumatology (ACR) criteria and 44 healthy subjects with no history of rheumatologic disease. To measure the level of 25-hydroxy vitamin D, venous blood samples (5 cc) were taken from each participant and the activity of the lupus disease was measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scale. Finally, the chi-square test, independent sample *t* test, one-way ANOVA, and multiple linear regression analysis were used to measure multivariate effects. The level of significance was set to be $P < 0.05$.

Results: Thirty-five lupus patients and 40 healthy subjects were females ($P = 0.847$). Vitamin D deficiency was observed in the case (42.1%) and control (11.4%) groups. The mean value of serum vitamin D3 level was 35.3 ng/mL in the control group, as well as 24.6 ng/mL and 21.3 ng/mL in patients with mild and severe SLE, respectively ($P = 0.024$).

Conclusion: In this study, high levels of 25-hydroxy vitamin D were observed among the healthy subjects compared to patients with SLE. Eventually, the level of vitamin D significantly decreased by increasing the severity of SLE activity.

Keywords: Systemic lupus erythematosus, Vitamin D, 25-hydroxy vitamin D, SLE activity

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Introduction

The systemic lupus erythematosus (SLE) is considered as a systemic autoimmune disease that involves different organs. It has different clinical manifestations from the skin and simple dermatologic and joint signs to life-threatening disorders such as renal, cardiovascular, and neurological complications. The most important manifestation of this disease is renal involvement or lupus nephritis, which is reported in many patients (40%-50%). The disease occurs throughout the world although its prevalence and severity vary in different societies. Over the past 50 years, the incidence of SLE has increased up to 10 times.^{1,2} However, there is no definite cure for the disease and it is generally inhibited by corticosteroids and immunosuppressive drugs.²

Various factors including genetic background, environmental factors, gender, hormonal factors, and viral infections contribute to the incidence and exacerbation of the disease. Recent studies have indicated the role of

vitamin D deficiency in the development of autoimmune and malignant diseases.² It should be noted that individuals with SLE are recommended to avoid sunlight in order to prevent skin rash and disease exacerbation, which reduces the serum concentration of vitamin D in these persons.³

Cholecalciferol is made from 7-dehydrocholesterol by UV rays in the skin. Some foods like egg yolk and fish oil are the sources of vitamin D3.⁴ The level of vitamin D in the body is associated with the season and its lowest and highest levels are observed in winter and at the end of the summer, respectively.⁵

Vitamin D is effective in regulating calcium absorption through endocrine mechanisms and expressing the genes through autocrine mechanisms.⁶ Vitamin D deficiency is also associated with the high risk of rickets in children and osteomalacia in adults, as well as bone fracture, cancer, autoimmune diseases, infectious diseases, diabetes type I and II, hypertension, heart disease, and multiple sclerosis.⁷ Some studies have shown that the increased vitamin D3

concentration enhances telomere length in leukocytes, resulting in a longer lifespan of leukocytes and preventing inflammatory diseases.⁸

In addition, vitamin D metabolites and vitamin D receptors exist in a variety of cells including immune system cells containing antigen-presenting cells, T lymphocyte cells, B lymphocyte cells, and monocytes. Recent studies have demonstrated several direct effects of calcitriol on the homeostasis of B cells, including the inhibition of memory and plasma cell production and an increase in the apoptosis of antibody-producing B cells. Such a cellular immune control is of paramount importance in autoimmune diseases.⁵ Some studies have reported low levels of vitamin D in SLE patients compared to non-SLE patients.^{9,10} A study also claimed a reduction in vitamin D as a risk factor for SLE patients and found that its enhanced reception prevents SLE and rheumatoid arthritis.^{11,12} In some studies, there has been a reverse relationship between serum vitamin D3 levels and SLE activity.^{11,13,14}

On the other hand, some studies indicated that vitamin D deficiency was not associated with the duration of the disease and its severity.^{2,3} Considering limited studies and inconsistent findings on the relationship between serum vitamin D levels and the SLE activity, as well as different complications of this disease for the patient, the current study sought to determine the relationship between vitamin D level and SLE activity. If such a relationship is proved, treatment with vitamin D is much easier than treatment with immunosuppressive drugs.

Materials and Methods

Design

This case-control study was conducted on 38 patients with SLE on the basis of the ACR criteria and 44 healthy subjects with no history of rheumatologic diseases. The participants in the control group were referred from the Internal Medicine Clinics, had no diagnosed rheumatologic and autoimmune diseases, received no vitamin D supplementation, and were at the premenopausal age.

Data Collection Method

Having received sufficient description by the physician and had informed consent, all participants were included in the study and evaluated clinically and in a laboratory. Venous blood samples (5 cc) were taken and sent to a laboratory in order to measure their 25-hydroxy vitamin D level and serum creatinine. Further, 25-hydroxy vitamin D was measured by the Corgeh Mix kit (Germany) through using the enzyme-linked immunosorbent assay (ELISA) method. D3 levels above 30 ng/mL and 30-16 ng/mL, and below 15 ng/mL were considered as normal, insufficiency, and deficiency.^{15,16} Furthermore, the creatinine level was measured with Pars Azmoon kit (Iran) by using the

biochemical method, followed by calculating the activity of SLE by using the standard SLEDAI instrument based on clinical and laboratory findings. Regarding this scale, the scores below 6 and 6-12, and above 12 were also considered as inactive, mild, and severe diseases, respectively.

Data Analysis

First, the Kolmogorov-Smirnov test was employed to test the normality of vitamin D3 and blood creatinine data. Then, the mean and standard deviation of these indices were calculated and an independent *t* test was run as well. Moreover, chi-square and Fisher exact tests were used to examine the relationship between qualitative variables. Finally, multiple linear regression analysis was utilized to measure multivariate effects.

Results

This study was performed on 38 patients with SLE as the case group and 44 healthy subjects as the control group. Three subjects (9.1%) in the control group and 3 cases (7.9%) in the SLE group were males ($P=0.847$). The mean ages of the participants in the control and case groups were 34.9 ± 15.9 and 35.7 ± 11.9 years, respectively ($P=0.787$). The mean serum creatinine level was 0.93 and 0.85 in case and control groups, respectively ($P=0.013$). The subjects in the case group had vitamin D3 deficiency (42.1%) and vitamin D3 insufficiency (28.9%). The corresponding values in the control group were 11.4% and 47.7%, respectively ($P=0.006$), the details of which are presented in Table 1.

The most common clinical signs included arthralgia (36.8%), arthritis (31.6%), photosensitivity (31.6%), anemia (71.1%), and edema (23.7%). Moreover, the most common paraclinical findings were anti-dsDNA

Table 1. Frequency, Mean, and Standard Deviation of Demographic and Clinical Characteristics of the Two Study Groups

Variables	Groups		P Value
	Case	Control	
Sex (f/m)	35.3	40.4	NS
Age (y)	35.7 ± 11.9	34.9 ± 15.9	0.787
Creatinine (mg/dL)	0.93 ± 0.16	0.85 ± 0.13	0.013
Vitamin D3 (ng/mL)			
Deficiency	16 (42.1)	5 (11.4)	0.006
Insufficiency	11 (28.9)	21 (47.7)	
Normal	11 (28.9)	18 (40.9)	
Mean \pm SD	23.3 ± 15.8	35.3 ± 22.4	0.007
Severity of SLE			
Mild	23 (60.5)	-	-
Moderate	15 (39.5)	-	-
Disease duration (months)	4.08 ± 4.7		

Note. SLE: Systemic lupus erythematosus

Table 2. Distribution Table of Vitamin D Serum Level With Severity of Lupus

Severity of Disease	Vitamin D3 Level				Mean ± SD
	Deficiency	Insufficient	Sufficient	Total	
Healthy group (control)	5 (11.4)	21 (47.7)	18 (40.9)	44	35.3 ± 22.4
Severity of SLE					
Mild	9 (39.1)	8 (34.8)	6 (26.1)	23	24.6 ± 16.4
Moderate	7 (46.7)	3 (20)	5 (33.3)	15	21.3 ± 15.1
Case	16 (42.1)	11 (28.9)	11 (28.9)	38	23.3 ± 15.8
<i>P</i> value	<i>P</i> ¹ = 0.026			<i>P</i> ² = 0.024	

Note. SLE: Systemic lupus erythematosus

*P*¹: based on chi square test

*P*²: based on oneway Anova test

(84.3%), antinuclear antibody (81.4%), complement deficiency, positive antiphospholipid, and high erythrocyte sedimentation rate (18.4%). The related data are shown in Figure 1.

In patients with severe and mild SLE, vitamin D3 deficiency was observed in 46.7% and 39.1% of patients, respectively. There was a statistically significant relationship between the severity of the disease and the vitamin D3 level ($P=0.026$). Additionally, the mean serum vitamin D3 level was 35.3 ng/mL in the control group, along with 24.6 and 21.3 ng/mL in patients with mild and severe SLE, respectively. In addition, a significant difference ($P=0.024$) was found between these groups regarding the vitamin D3 level (Table 2).

Further, multiple linear regression analysis was used for multivariate analysis. The results of this model reflected the significant effects of the disease on the vitamin D level, indicating that the severity of the disease enhances as the vitamin D level decreases ($B = -7.019$). This model had a relatively high explanatory power (adjusted R square=0.64). The obtained data are summarized in Table 3.

Discussion

In this study, serum vitamin D3 level and the disease activity were compared in 38 patients with SLE and 44 healthy individuals. The vitamin D3 deficiency was diagnosed in 42.1% of the patients and 11.4% of healthy subjects ($P=0.006$). Furthermore, the mean serum vitamin D3 level was 23.3 ng/mL for the patients and 35.3 ng/mL for the healthy group. However, these values were 24.6 ng/mL and 21.3 ng/mL in patients with mild and severe SLE. Accordingly, a significant difference was observed between the groups regarding the vitamin D3 level ($P=0.024$), showing a significant relationship between vitamin D3 level and SLE activity. Contrarily, no relationship was observed between vitamin D deficiency and the levels of albumin, creatinine, hemoglobin, anti-dsDNA titer, and complements level, namely, C3, C4, and CH50 ($P > 0.05$). Photosensitivity was also reported in 31.6% of the patients.

Some studies have supported the relationship between

vitamin D3 deficiency and SLE. For instance, Toloza et al evaluated patients with SLE and found a correlation between vitamin D deficiency and clinical manifestations and SLE disease activity.³ In the present study, the high prevalence of vitamin D deficiency in patients (42.1%) and its low prevalence in healthy subjects (11.4%) can highlight the role of vitamin D3 in the pathogenesis and severity of the SLE disease.

In another study, Toloza et al reported vitamin D3 deficiency and insufficiency in 17.9% and 66.7% of the patients.³ Moreover, Abou-Raya indicated that the mean vitamin D level was 19.8 ng/mL among the patients and 28.7 ng/mL in the control group.¹² Ruiz-Iratorza et al also examined 92 SLE patients, of whom 75% had vitamin D3 deficiency and 15% had vitamin D3 insufficiency. Photosensitivity was observed in 68% of the patients as well.¹⁷

The prevalence of vitamin D3 deficiency in the above-mentioned study was greater compared to the present study, which can be due to the high photosensitivity reported in the present study. Reduced photosensitivity can provide more exposure to sunlight and reduce the likelihood of vitamin D3 deficiency.²

Additionally, Szodoray et al conducted a study on 177 patients with SLE and found that the mean vitamin D3 level was 13.2±6.28 ng/mL. Further, the prevalence of vitamin D3 insufficiency and deficiency was observed in 44.6% and 37.3% of the patients.¹⁸ These findings are

Table 3. Regression Parameters in the Estimation of Vitamin D Level Based on the Predictors

Variables	Unstandardized Coefficients		<i>P</i> Value
	B	Standard Error	
(Constant)	49.757	14.608	3.406 0.001
Gender	-6.037	7.818	-0.772 0.442
Age	0.042	0.156	0.267 0.790
Creatinine level	-18.519	15.274	-1.213 0.229
SLE activity	-7.019	2.891	-2.428 0.018

Adjusted R Square = 0.64

Note. SLE: Systemic lupus erythematosus.

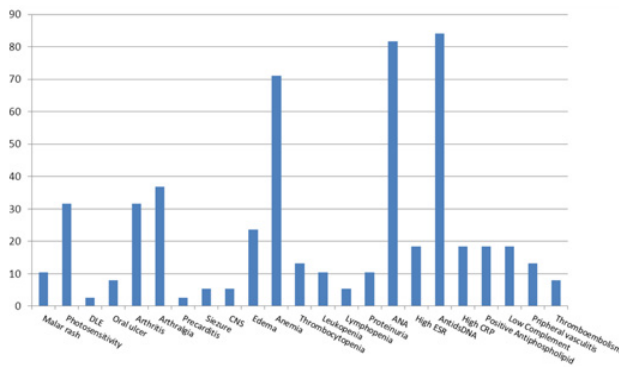


Figure 1. Clinical Sign and Symptoms of Lupus Patients.

consistent with those of the present study. In a systematic review, a relationship was highlighted between vitamin D3 deficiency and SLE, and sufficient evidence was presented to support the correlation between vitamin D3 and SLE. However, the relationship between vitamin D3 deficiency and other clinical features of the disease should be concerned in future studies.¹⁹ In addition, it is clear that there is an active vitamin D metabolism by immune cells, which is able to locally convert 25(OH)D3 into 1,25(OH)2D3, as its active form. Vitamin D and vitamin D receptor signaling together have a suppressive role in autoimmunity as well as an anti-inflammatory effect.²⁰

There are some inconsistencies regarding the findings of some studies conducted to determine the relationship between vitamin D3 level and the SLE activity. For example, Bonakdar et al observed a significant relationship between vitamin D3 deficiency and SLE activity at the onset of the disease as well as a more severe vitamin D3 deficiency with low albumin and hemoglobin levels with higher anti-dsDNA titer.²¹ However, Kim et al reported no association between serum vitamin D3 level and disease activity with respect to the SLE disease activity index and anti-dsDNA level, even though a positive correlation was found between the vitamin D3 level and hemoglobin and complement.²² In another study, Ruiz-Irastorza et al noticed no significant relationship between the vitamin D3 level and the severity of SLE, but a significant correlation between vitamin D3 deficiency and fatigue.¹⁷ Furthermore, the present study examined the effects of disease severity on vitamin D3 levels by eliminating the effect of confounder factors using multiple linear regression models. The only factor affecting the vitamin D3 level in this model was the severity of SLE activity. In other words, it can be concluded that a decrease in vitamin D3 levels leads to an increase in disease severity. Differences in the vitamin D3 level for the SLE and healthy groups can be the result of the high prevalence of photosensitivity in SLE patients, high use of sunscreen, and the consumption of steroids for the treatment and control of the disease. In Iran and other Islamic countries, women's veils also reduce

skin exposure to sunlight, leading to a higher prevalence of vitamin D3 deficiency. Thus, studies with larger sample sizes and sample homogeneity in terms of age and gender are recommended to reveal the true association between vitamin D3 deficiency and SLE disease.

Of subjects, 11.4% experienced vitamin D3 deficiency and 47.7% had vitamin D3 insufficiency although these values were 39.1% and 34.8% in patients with mild activity, as well as 46.7% and 20% in patients with severe activity, respectively. The findings implied an increased percentage of vitamin D3 deficiency by an increase in disease activity ($P=0.026$). In the study by Mok et al on 376 SLE patients, the 25-hydroxy vitamin D level was below 15 ng/mL in 26%, 15-30 ng/mL in 54%, and above 30 ng/mL in 20% of the patients and the vitamin D3 deficiency was associated with disease severity and its tendency to relapse.²³ Likewise, Cutolo et al measured serum vitamin D3 levels in 21 patients with SLE activity using ECLAM and SLEDAI. The results showed that serum vitamin D3 level in SLE patients was lower compared to the healthy group and the severity of SLE was inversely correlated with serum vitamin D3 level.¹¹ In a cohort study by Amital et al, 378 patients with SLE were selected and the disease activity was measured using ECLAM and SLEDAI, followed by measuring serum 25-hydroxy vitamin D concentration in these patients. The findings revealed a reverse relationship between serum vitamin D3 concentration and SLE activity.¹³

Conclusion

In this study, high levels of 25-hydroxy vitamin D were observed in healthy subjects compared to patients with SLE, and the vitamin D3 level significantly decreased with a significant increase in the SLE activity.

Ethical Approval

The present project has been approved by ethical committee of kashan university of medical sciences (ID number=IR.KAUMS.REC.1394.123).

Conflict of Interest Disclosures

The authors declare no conflict of interests.

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