

Vitamin D levels in systematic lupus erythematosus patients: association with disease activity index and interferon alpha

Afsaneh Enteshari-moghaddam, Gholamreza Ravaei, Ahad Azami*

Department of Internal Medicine, Ardabil University of Medical Science, Ardabil, Iran

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***Correspondence to:**

Dr. Ahad Azami,
Email: ahadazami45@gmail.com

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ABSTRACT

Background: In different studies the correlation between systemic lupus erythematosus (SLE) and disease activity with vitamin D has been shown. The role of different interferons especially interferon alpha (IFN- α) in lupus pathogenesis have been previously shown. Considering the role of vitamin D and IFN- α , it is possible that these two could demonstrate the SLE activity. This study aimed to investigate the association between vitamin D levels and IFN- α with disease activity index in Ardabil city SLE patients.

Methods: In this case control study, 50 SLE patients and 50 age and sex matched healthy subjects were recruited. Patients had serum 25-OH Vitamin D concentration and disease activity recorded. Vitamin D and IFN- α levels were compared between two groups and also, levels of anti-dsDNA, and SLEDAI in case group was measured. Statistical methods were used to determine the correlation between vitamin D and IFN- α with disease activity index at baseline.

Results: Vitamin D deficiency (<40 nmol/L) was detected in 20% of SLE patients. Vitamin D level in case group significantly lower than control group (23.94 \pm 11.93 vs. 29.10 \pm 11.40 ng/ml, p=0.02). The IFN- α amount in case group significantly upper than control group (396.60 \pm 54.73 vs. 200.38 \pm 14.42, p=0.001). There was significantly negative correlation between vitamin D with IFN- α (r=-0.413, p=0.003), SLEDAI (r=-0.492, p<0.001) and anti-dsDNA (r=-0.417, p=0.003). There was positive correlation between IFN- α with SLEDAI (r=0.358, p=0.01) and anti-dsDNA (p=0.297, p=0.03).

Conclusions: Results showed that the low vitamin D was associated with a higher disease activity in SLE patients. Also, it seems that, the improvement of vitamin D levels by decreasing IFN- α could help in controlling disease activity in future.

Keywords: Disease activity, Interferon alpha, Systemic Lupus Erythematosus, Vitamin D

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmunity with unknown etiology and continuous relapse periods depending on several factors including environmental and host genetics.¹ Patients with SLE have an immune response against different intercellular antigens leading to immune complexes and sediments in vascular parts of different body organs. Immune sediments cause local inflammation and tissue damage that leading to heightening auto-immune response. Patients with SLE cause an immune response against a variety of antigens. This response leads to the creation of immune complexes

that precipitate in various vascular organs of the body. Sedimentation of the immune complexes causes local inflammation and tissue damage that may aggravate the immune response.²

In recent studies, there was particular attention to levels of vitamin D and its role in different diseases. It has been observed that vitamin D levels is associated with some of chronic diseases such as cardiovascular diseases, malignancy and many other autoimmunity diseases such as type 1 diabetes mellitus, inflammatory bowel disease (IBD), Multiple Sclerosis, undifferentiated connective tissue disease, rheumatoid arthritis (RA) and SLE.³ It is

also observed that serum vitamin D levels has a reverse relationship with SLE activity scores.^{4,6}

Vitamin D is a steroid hormone that plays an important role in calcium metabolism and bone homeostasis, by binding to the intracellular vitamin D receptor (VDR) in target tissues such as the gastrointestinal tract, kidneys, bones, parathyroid glands and skin. It exists in two physiological forms, vitamin D₂ and vitamin D₃. The primary source (80%) of vitamin D is the synthesis of vitamin D₃ in the skin upon exposure to UVB radiation. Vitamin D₃ is then metabolized in the liver to 25-hydroxyvitamin D (25(OH) D), which is the intermediate usually measured to determine a patient's vitamin D status. 25 (OH) D is further metabolized in the kidneys to the active form, 1, 25-dihydroxy vitamin D.⁷

Recent studies showed that vitamin D had main role in the physiologic condition of body and its deficiency related with chronic diseases such as calcium disorders, cancers, cardiovascular diseases and auto-immune diseases.⁸⁻⁹

Many studies recently done on the role of vitamin D in the modulating the activity of the immune system.¹⁰⁻¹²

According to the Shoenfeld et al, study in recent years evidence has accumulated regarding the effect of vitamin D on the immune system and its different cells. Some studies have noted lower vitamin D concentrations in patients with SLE but these epidemiological not answer the exact response to the hypothesis of vitamin D role in SLE.¹³

Vitamin D may be considered as a pro-hormone which is obtained from 2 distinct sources; to a lesser extent diet, but principally by synthesis in the epidermal layer of the skin after UV exposure. In the skin, UV rays promote photolytic cleavage of 7-dihydrocholesterol into pre-vitamin D, which is subsequently converted by spontaneous thermal isomerization into vitamin D₃.¹⁴

Interferon has been vastly evaluated in lupus pathogenesis during past recent years. IFN- α is a pleiotropic cytokine influencing different kinds of cells in lupus. High levels of IFN- α in patient with SLE has been reported comparing with healthy people.¹⁵⁻¹⁸ IFN- α is able to affect production, progression and pathogenesis of SLE as it influences the function and activation level of main immunity cells and acts as a bridge between innate and acquired immunity.¹⁵

Vitamin D supplementation in SLE patients was associated with decrease in inflammatory cytokines and markers: IL-1, IL-6, IL-18, TNF- α , erythrocyte sedimentation rate (ESR); vitamin D supplementation was also associated with a reduction in autoantibodies and elevation in complement level.^{19,20} Vitamin D treatment enhanced T-reg cells and production of T helper 2 cytokines; a correlation was found between disease activity and change in 25(OH)D in deficient patients following treatment; and vitamin D treatment even showed

improvement in disease activity and fatigue among juvenile-onset SLE.²¹⁻²³

IFN- α can be a marker of disease activity and low levels in treated patients can express the response to treatment. Vitamin D levels have reverse relationship with disease activity. So, it is possible that there would be a relationship between IFN- α levels and vitamin D levels in patients with SLE. There is only one study investigating this relationship and expressing that there is an obvious negative relationship between vitamin D levels and IFN- α level, so that with high level of vitamin D, IFN- α is low and disease has lower activity.²⁴ This study aims at investigating the relationship between vitamin D and IFN- α level with disease activity in SLE patients.

METHODS

This is a case-control study which was approved in code IR.ARUMS.REC.169 by Ardabil University of Medical Science ethics committee and carried out on 50 patients with lupus and 50 healthy people in Imam Khomeini Hospital in Ardabil. All patients provided written informed consent and measurement of 25-OH vitamin D level and definition of insufficiency were taken from all participants.

Inclusion criteria

For this study, authors recruited all patients who fulfilled the revised American College of Rheumatology (ACR) criteria for the classification of SLE. Control cases selected from all patients without any history of auto-immune diseases.

Measurement of vitamin D and INT- α

The serum vitamin D were measured by ELISA kit related to the Euroimmun lübeck from Germany country and serum interferon alpha levels were measured by the ELISA of Bender MedSystems, Inc. Burlingame, California. All measurements done by the guideline of each manufactory.

Measurement of disease activity index

Authors used the systemic lupus erythematosus disease activity index (SLEDAI) questionnaire for diseases activity index which had score between 1 and 8 based on clinical examination by a clinician and occurrence of some disorders.

Statistical analysis

Collected data were analysed using descriptive statistical methods (frequency, percentage, Mean \pm SD). Also, authors checked the normality of distribution for all data by K-S test and then authors used Pearson correlation test and scatter plot for obtain the relationship between quantitative variables such as 25-Oh vitamin D and dsDNA, SLEDAI scores and INF- α . A p<0.05 was

considered as significant. All data analysed in SPSS version 16.

RESULTS

In this paper, 50 patients with SLE and 50 healthy people were evaluated that they are matched. Of all patients, 84% were female and 16% were male. The mean of 25(OH) vitamin D and rate of normal vitamin D in case group significantly lower than control group (Table 1). The mean of vitamin D and INF- α among male and females in case group was 21.82 \pm 9.75 and 24.18 \pm 12.21ng/ml, respectively and the difference between two genders wasn't significant.

Table 1: Clinical characteristics of SLE patients and healthy controls.

Variables	SLE	Healthy controls	p-value
Age (year)	33.74 \pm 9.12	36.76 \pm 8.88	0.09
Sex (m/f)	5/45	11/39	0.1
Vitamin D (ng/ml)	23.94 \pm 11.93	29.1 \pm 11.4	0.02
INF- α	396.6 \pm 54.73	200.38 \pm 14.43	0.001
Vitamin D levels			
Normal	10 (20%)	20 (40%)	0.06
Insufficient	39 (78%)	30 (60%)	
Deficient	1 (2%)	-	
SLEDAI			
Mean	9.46 \pm 6.52	-	
Median	8		
Range	0-28		

The mean level of INF- α in case group with 396.60 \pm 54.73pg/ml significantly higher than control group with 200.38 \pm 14.42pg/ml (P=0.001).

INF- α level of male and females of case group was 221.60 \pm 25.00 and 416.04 \pm 60.12pg/ml, respectively that shows no meaningful difference.

Table 2: Correlation between Vitamin D level and INF- α and clinical characteristics of SLE patients.

Variables	With Vitamin D		With INF- α	
	r	p-value	r	p-value
INF- α	-0.413	0.003		
SLEDAI	-0.492	0.001	0.358	0.01
Anti-dsDNA	-0.417	0.003	0.297	0.03

There was a meaningful reverse correlation between vitamin D level and INF- α level (Figure 1), SLEDAI (Figure 2). There was a meaningful indirect relationship between INF- α level, SLEDAI, anti-dsDNA level with Vitamin D. Also, there was a direct meaningful relationship between INF- α level and SLEDAI and anti-dsDNA level. However, no meaningful relationship was

observed between vitamin D and INF- α level in control group but the relationship between vitamin D and INF- α in SLE patients was indirect and significant. (r=-0.413, p=0.003) also the correlation between SLEDAI and INF- α in SLE patients was positive and significant (r=0.358, p=0.001) (Table 2).

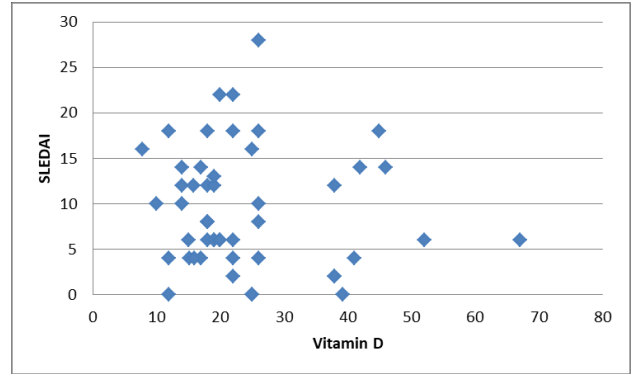


Figure 1: Correlation between vitamin D and INF- α .

SLE people with normal vitamin D level had meaningfully lower INF- α level, SLEDAI, than people with insufficient Vitamin D. Also, we observed that the mean of SLEDAI score in SLE people with normal vitamin D level with 3.2 \pm 1.23 significantly lower than healthy people with 10.4 \pm 5.2 (p=0.001).

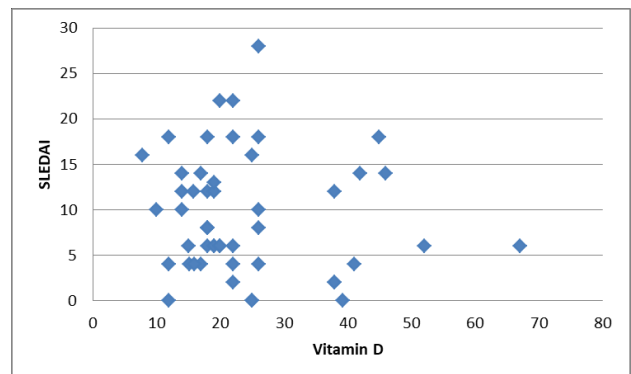


Figure 2: Correlation between vitamin D and SLEDAI.

Table 3: Clinical characteristics of SLE patients by level of vitamin D.

Vitamin D levels variables	Normal	Insufficient	p-value
age	32.4 \pm 6.7	34.4 \pm 9.6	0.54
Sex			
Male	1 (10%)	4 (10.3%)	0.98
Female	9 (90%)	35 (89.7%)	
INF- α	164.4 \pm 19.85	437.5 \pm 64.5	0.03
SLEDAI	3.2 \pm 1.23	10.4 \pm 5.2	0.001
Anti-ds DNA	15.9 \pm 7.37	59.5 \pm 6.6	0.002

Also, authors observed that the mean of INF- α in SLE people with normal vitamin D level with 164.4 ± 19.85 significantly lower than SLE people with Insufficient vitamin D level with 437.5 ± 64.5 . ($p=0.03$) (Table 3).

DISCUSSION

In this study, it is observed that SLE patients had lower vitamin D3 levels than healthy people and also there was a significant relationship between high levels of IFN- α with SLEDAI and anti-dsDNA.

It is also observed that 20% of SLE patients had normal vitamin D level, 78% had insufficiency and only 2% had deficiency. Low levels of vitamin D in SLE patients has been reported in Schoindre et al, study that reported vitamin D deficiency in 15.9% and insufficiency in 65.9% of SLE patients.⁴ As vitamin D deficient cases were few in our group but the total rate of vitamin D deficiency was equal in both groups. A recent report showed an approximate vitamin D3 deficiency in two third and deficiency (less than 10 ng/ml) in about one fifth of SLE patients.²⁵

Low levels of vitamin D3 in SLE patients comparing healthy people was reported in different societies.²⁶ In present study, it is observed that lupus patients significantly had lower vitamin D level than healthy people in control group. Normal level vitamin D in SLE patients was lower than control group. Similarly, Hamza et al, observed that vitamin D levels in SLE patients were significantly lower than control group.⁶

Vitamin D insufficiency is a common finding among Iranians. In a review study, Heshmat et al, expressed that vitamin D insufficiency in Iranian males and females have been %76.1 and %72.1, respectively.¹⁵ Based on different studies, vitamin D insufficiency varies in different parts of country which can explained through geographical and local situation, kind of clothing and nutrition in each area.²⁷⁻³²

Low levels of vitamin D could not be a factor for producing and progressing SLE, but its low levels can worsen the disease. In present study, a meaningful negative correlation was observed between vitamin D level and SLEDAI ($r=-0.492$, $p=0.001$). Low levels of vitamin D are associated with higher SLEDAI ($r=-0.492$, $p=0.001$) and higher anti-dsDNA levels ($r=-0.417$, $p=0.003$).

Previous studies expressed that vitamin D3 levels had a reverse relationship with SLE disease activity index (SLEDAI).⁵⁻⁷ Sumethkul et al, Hamza et al, and Schoindre et al, observed that low vitamin D level had a meaningful reverse correlation with higher SLEDAI.^{4,6,33} Also, Mandal et al, in a study showed that vitamin D level had a meaningfully reverse correlation with SLEDAI and anti-dsDNA.²⁴ Also, in some studies, no relationship was reported between vitamin D level and SLEDAI score.³⁴⁻³⁷

The role of IFN- α has recently investigated in pathogenesis of SLE. Some studies demonstrated a very strong relationship between IFN- α in presence of autoantibodies related to SLE such as anti-La, anti-To, anti-Sm, anti-Rnp and anti-dsDNA.^{38,39} Lupus patients with high serum level of IFN- α had significantly skin and kidney diseases in most of the studies.^{17,18,39}

Some of the studies showed that IFN- α is related to disease activity so, that IFN- α can detect patients with high disease activity comparing to other patients.^{17,18,39,40} It is observed that patients with SLE had meaningfully higher IFN- α level than healthy people. Also, IFN- α levels had a positive correlation with SLEDAI ($r=0.35$, $p=0.01$) and anti-dsDNA ($r=0.297$, $p=0.03$).

Similarly, Dall'era et al, observed that interferon levels have meaningful and direct relationship with SLEDAI and anti-dsDNA levels and a reverse relationship with C3 levels.¹⁷ Kirou et al, expressed that patients with SLE with high IFN- α have higher disease activity index. Also, high levels of interferon may lead lower levels of C3 expressing increased activity of disease and higher ESR and anti-dsDNA.¹⁷ Mandal et al, observed that patients with SLE resistant to treatment had meaningfully higher plasmatic IFN- α levels than treating patients and control group. Also, Kareem et al, in a study showed that lower levels of vitamin D correlated with higher ESR in all patients and with the SLEDAI score.⁴¹

However, in some other studies has been expressed that IFN- α levels had no relationship with disease activity. Oke et al, stated that high levels of interferon do not seem to be a specialized biomarker for SLE.⁴² Moreover, Jolly et al, observed no meaningful relationship between IFN- α activity with disease activity.⁴³

It is observed that in different studies, the IFN- α and vitamin D levels in patients with SLE are higher than healthy people and also related to different disease activity and markers. Therefore, it is possible that these two markers are connected. In present study, there is meaningful negative correlation between vitamin D and IFN- α levels. Similarly, Mandal et al, reported a strong negative correlation between vitamin D and IFN- α .²⁴ Ritterhouse et al, observed that patients with vitamin D deficiency have higher serum IFN- α activity comparing to people without vitamin D deficiency.⁴⁴ In this study case-control study we not separated the cases with active disease from case with controlled disease, so authors could not state certainty the role of low level of vitamin D in these two groups. Another limitation of this study was the low sample size

CONCLUSION

Results showed that vitamin D and INF-a have main role in diseases activity in SLE patients and it seem that improvement status of vitamin D by reducing the INF-a levels could be effective in control the severity of disease.

Recommendations

According to the results of this study, the measure of vitamin D in all SLE patients recommended and in all patients with a low level of vitamin D, starting treatment has been recommended for improve their condition and accompanying symptoms.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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