

Relationship between Serum Vitamin D Level, Interferon Alpha and Psychological Disorders in Patients with SLE (Systemic Lupus Erythematosus)

Afsaneh Enteshari-Moghaddam¹, Ahad Azami^{1*}, Yusef Mohammadi-Kebar¹ and Saeid Sadeghieh-Ahari²

¹Department of Internal Medicine, Faculty of Medicine, Ardabil University of Medical Science, Ardabil, Iran

²Department of Community Medicine, Faculty of Medicine, Ardabil University of Medical Science, Ardabil, Iran

Article Information

Received date: Nov 27, 2018

Accepted date: May 27, 2019

Published date: May 29, 2019

*Corresponding author

Ahad Azami, Department of Internal Medicine, Ardabil University of Medical Science, Iran,
Email: a.azami@arums.ac.ir

Distributed under Creative Commons CC-BY 4.0

Keywords Systemic lupus erythematosus; Vitamin D; Depression; Anxiety; Stress

Abstract

Background: In different studies, the correlation between systemic lupus erythematosus (SLE) and disease activity with vitamin D has been shown. Also, low level of vitamin D and interferon alpha was associated with psychological disorders but there wasn't more evidence about the relationship between vitamin D deficiency and psychological disorders.

Objective: This study aimed to investigate Relationship between serum vitamin D level, interferon alpha and psychological disorders in patients with SLE.

Methods: In this cross-sectional descriptive study, 50 SLE patients were recruited. Serum 25-OH Vitamin D concentration and IFN- α levels and also, levels of SLEDAI were measured. Statistical methods were used to determine the correlation between vitamin D and IFN- α and also the correlation between IFN- α with Depression, Stress and Anxiety scores in SLE patients.

Results: Vitamin D deficiency (<40 nmol/L) was detected in 20% of SLE patients. The mean Vitamin D and IFN- α in SLE patients was 23.94 ± 11.93 and 396.60 ± 54.73 , respectively. There was significantly negative correlation between vitamin D and depression ($r=-0.479$, $p=0.001$) and Anxiety ($r=-0.34$, $p=0.01$) but the relation between vitamin D and stress wasn't significant. Of all SLE patients, 56% had depression, 64% had anxiety and 66% had stress in very severe level.

Conclusion: Results showed that the level of vitamin D was negatively correlated with depression and anxiety of patients. Also, it seems that, by increasing the QOL of patients and decreasing the rate of depression and anxiety in SLE patients we could improve the vitamin D level and then SLEDAI.

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].

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 [7,8].

Many studies recently done on the role of vitamin D in the modulating the activity of the immune system [9-11].

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 [12,13]. 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 [14-16].

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 [17]. This study aims at investigating the relationship between vitamin D and IFN- α level with disease activity in SLE patients.

Material and Methods

Study design and population

This cross-sectional descriptive study was approved in code IR.ARUMS.REC.169 by Ardabil University of Medical Science ethics committee in Ardabil a province in northwest of Iran and carried out on 50 patients with lupus 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 and exclusion criteria

For this study, we recruited all patients who fulfilled the revised American College of Rheumatology (ACR) criteria for the classification of SLE.

Table 1: The levels of Anxiety, stress and depression in SLE patients.

| Variables | Levels | Case group (n, %) |
|------------|-------------|-------------------|
| Depression | Normal | 12(24) |
| | Mild | 1(2) |
| | Severe | 9(18) |
| | Very severe | 28(56) |
| | Normal | 4(8) |
| Anxiety | Mild | 1(2) |
| | Moderate | 9(18) |
| | Severe | 4(8) |
| | Very severe | 32(64) |
| | Normal | 6(12) |
| Stress | Mild | 2(4) |
| | Moderate | 2(4) |
| | Severe | 7(14) |
| | Very severe | 33(66) |

Measurement of vitamin D

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. The amount of Vitamin D less than 30 ng/mL were considered as a deficiency.

Measurement of disease activity index SLEDAI

We 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.

Measurement of Depression, stress and anxiety

We used the Depression Anxiety Stress Scales (DASS) standard questionnaire included 21 questions for depression, anxiety and stress each with 7 item and each item scored between 0 to 3 and their levels classified from normal to very severe based on scores.

Statistical analysis

Collected data were analyzed using descriptive statistical methods (frequency, percentage, Mean \pm SD). Also we checked the normality of distribution for all data by K-S test and then we used Pearson correlation test and scatter plot for obtain the relationship between quantitative variables such as 25-Oh Vitamin D and dsDNA, SLEDAI scores, DASS21 and INF- α . A $p < 0.05$ was considered as significant. All data analyzed in SPSS version 16.

Ethical Approve

This study financially supported by Ardabil University of Medical Science and approve in the ethical committee and registered by code IR.ARUMS.REC.2017.169.

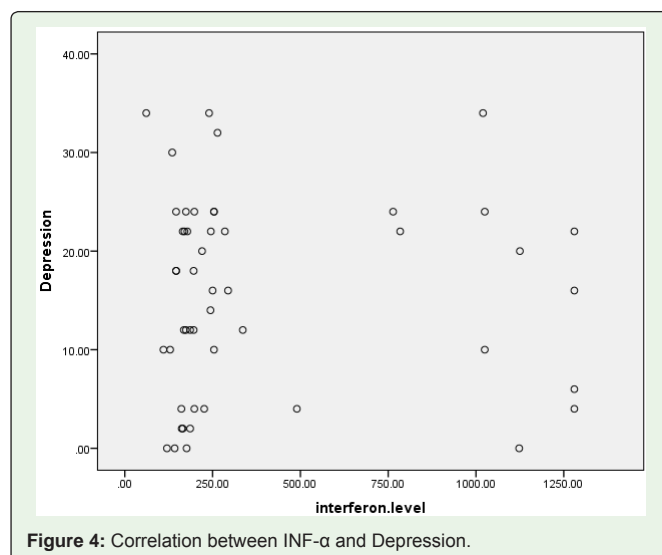
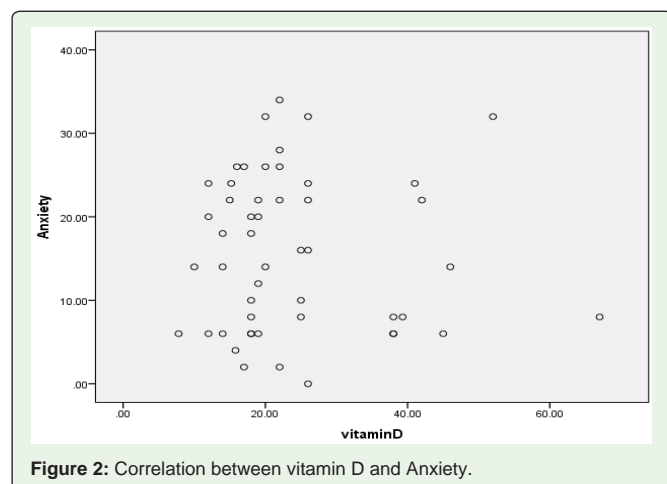
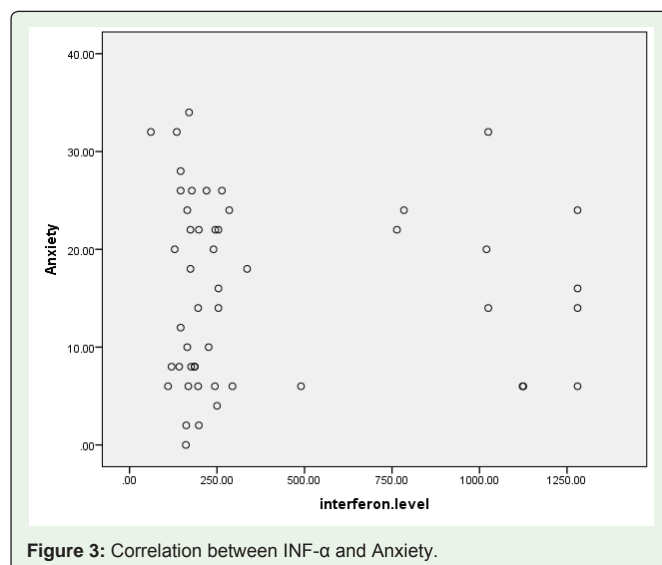
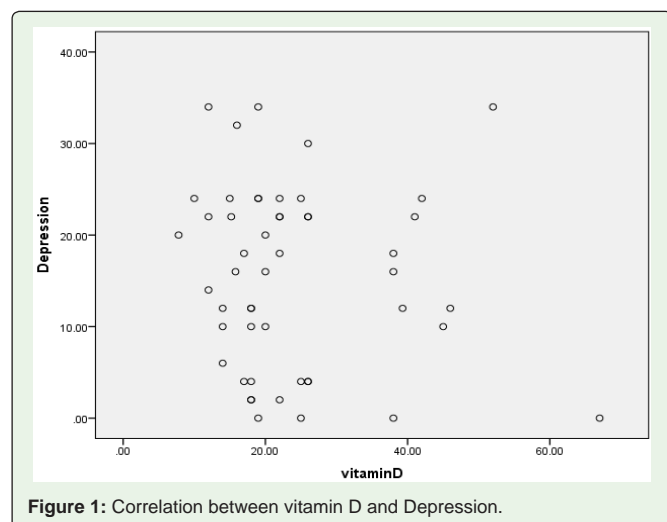
Results

In this research, 50 patients with SLE were evaluated. The mean of depression, anxiety and stress based on DASS21 was 15.5 ± 9.9 , 15.7 ± 9.3 and 18.8 ± 9.1 , respectively. Most of cases had depression, stress and anxiety in very severe level (Table 1).

There was a meaningful reverse correlation between vitamin D level and depression ($r = -0.479$, $p = 0.001$) and anxiety ($r = -0.34$, $p = 0.01$) but the correlation between INF- α and depression, stress, anxiety wasn't significant (Table 2 and Figures 1-4).

Table 2: Correlation between Vitamin D level 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 |
| Age | -0.02 | 0.8 | -0.16 | 0.3 |
| Depression | -0.479 | 0.001 | 0.004 | 0.98 |
| Anxiety | -0.34 | 0.01 | -0.008 | 0.96 |
| Stress | -0.22 | 0.1 | -0.017 | 0.91 |



Also, we observed that the mean of general depression score in SLE people with normal vitamin D level with 3.2 ± 1.23 significantly lower than SLE people with Insufficient vitamin D level with 17.5 ± 9.5 . ($p=0.03$) (Table 3).

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

| Vitamin D levels | | Normal | Insufficient | p-value |
|------------------------|-----|-------------|--------------|---------|
| Variables | | | | |
| Age | | 32.4±6.7 | 34.4±9.6 | 0.54 |
| M | Sex | 1 (10%) | 4 (10.3%) | 0.98 |
| F | | 9 (90%) | 35 (89.7%) | |
| INF-α | | 164.4±19.85 | 437.5±64.5 | 0.03 |
| SLEDAI | | 3.2±1.23 | 10.4±5.2 | 0.001 |
| Depression | | 3.2±1.23 | 17.5±9.5 | 0.003 |
| Anxiety | | 9.6±2.5 | 16.7±9.1 | 0.02 |
| Stress | | 14.6±12 | 19.8±8.1 | 0.11 |
| Low level of compliant | | 1(10%) | 22(56.4%) | 0.01 |

Discussion

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]. 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 [18].

Low levels of vitamin D3 in SLE patients comparing healthy people was reported in different societies [19]. In present study, it is observed that lupus patients significantly had lower vitamin D level than healthy people in society. Normal level vitamin D in SLE patients was lower than society. 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 expressed that vitamin D insufficiency in Iranian males and females have been 76.1% and 72.1%, respectively [20]. 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 [21-23].

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 ($r=-0.417$, $p=0.003$).

Sumethkul et al.[24], Hamza et al., [6] and Schoindre et al.[4] observed that low vitamin D level had a meaningful reverse correlation with higher SLEDAI. Also, Mandal et al in a study showed that vitamin D level had a meaningfully reverse correlation with SLEDAI and anti-dsDNA [17]. Also, in some studies, no relationship was reported between vitamin D and SLEDAI [25,26].

By studying the levels of depression, anxiety and stress in SLE patients and their relation with vitamin D and INF- α we observed that there was an inverse correlation between vitamin D and anxiety and depression rate but the correlation between INF- α and depression and anxiety wasn't significant. Gholamrezaei et al in a study showed that vitamin D level had significant correlation with physical activity index and anxiety of patients but not correlated with depression [27].

Studies showed that the vitamin D deficiency was more common among people with severe and very severe anxiety and after improvement the vitamin D level in these patients their depression and anxiety levels promoted [28].

A systematic review on SLE patients showed that prevalence of anxiety and depression in these patients were very high about twice more than society [29].

Sotodeh-Asl et al., in a study showed that there wasn't more evidence for determine the significant relationship between low level of vitamin D and psychological disorders which wasn't in line with our study results because in current study we showed that there was an inverse correlation between depression and anxiety and vitamin D levels [30].

Conclusions

Results showed that the level of vitamin D was negatively correlated with depression and anxiety of patients. Also, it seems that, by increasing the QOL of patients and decreasing the rate of depression and anxiety in SLE patients we could improve the vitamin D level and then SLEDAI.

Limitations

In this study case-control study we not separated the cases with active disease from case with controlled disease, so we could not stated certainty the role of low level of vitamin D in these two groups. Another limitation of this study was the low sample size.

Recommendation

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.

References

1. Crispin JC, Liossis SN, Kis-Toth K, Lieberman LA, Kyttaris VC, Juang YT, et al. Pathogenesis of human systemic lupus erythematosus: recent advances. *Trends Mol Med*. 2010; 16: 47-57.
2. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med*. 2011; 365: 2110-2121.
3. Petri M, Bello KJ, Fang H, Magder LS. Vitamin D in systemic lupus erythematosus: modest association with disease activity and the urine protein-to-creatinine ratio. *Arthritis Rheum*. 2013; 65: 1865-1871.
4. Borba VZ, Vieira JG, Kasamatsu T, Radominski SC, Sato EI, Lazaretti-Castro M. Vitamin D deficiency in patients with active systemic lupus erythematosus. *Osteoporos Int*. 2009; 20: 427-33.
5. Hamza RT, Awwad KS, Ali MK, Hamed AI. Reduced serum concentrations of 25-hydroxy vitamin D in Egyptian patients with systemic lupus erythematosus: relation to disease activity. *Med Sci Monit*. 2011; 17: 711-718.
6. Vacca A, Cormier C, Piras M, Mathieu A, Kahan A, Allanore Y. Vitamin D deficiency and insufficiency in 2 independent cohorts of patients with systemic sclerosis. *J Rheumatol*. 2009; 36: 1924-1929.
7. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007; 357: 266-281.
8. Holick MF. Vitamin D: important for prevention of osteoporosis, cardiovascular heart disease, type 1 diabetes, autoimmune diseases, and some cancers. *South Med J*. 2005; 98: 1024-1027.
9. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. *Curr Opin Pharmacol*. 2010; 10: 482-496.
10. Borges MC, Martini LA, Rogero MM. Current perspectives on vitamin D, immune system, and chronic diseases. *Nutrition*. 2011; 27: 399-404.
11. Cutolo M, Pizzorni C, Sulli A. Vitamin D endocrine system involvement in autoimmune rheumatic diseases. *Autoimmun Rev*. 2011; 11:84-87.
12. Abou-Raya A, Abou-Raya S, Helmii M. The effect of vitamin D supplementation on inflammatory and hemostatic markers and disease activity in patients with systemic lupus erythematosus: a randomized placebo-controlled trial. *J Rheumatol*. 2012; 40: 265-272.
13. Gurion R, Tangpricha V, Yow E, Schanberg LE, McCormsey GA, Robinson AB. Avascular necrosis in pediatric systemic lupus erythematosus: a brief report and review of the literature. *Pediatr Rheumatol*. 2015; 13: 13.
14. Piantoni S, Andreoli L, Scarsi M, Zanolà A, Dall'Ara F, Pizzorni C, et al. Phenotype modifications of T-cells and their shift toward a Th2 response

- in patients with systemic lupus erythematosus supplemented with different monthly regimens of vitamin D. *Lupus*. 2015; 24: 490-498.
15. Petri M, Bello KJ, Fang H, Magder LS. Vitamin D in systemic lupus erythematosus: modest association with disease activity and the urine protein-to-creatinine ratio. *Arthritis Rheum*. 2013; 65: 1865-1871.
 16. Lima GL, Paupitz J, Aikawa NE, Takayama L, Bonfa E, Pereira RMR. Vitamin D supplementation in adolescents and young adults with juvenile systemic lupus erythematosus for improvement in disease activity and fatigue scores: a randomized, doubleblind, placebo-controlled trial. *Arthritis Care Res*. 2016; 68: 91-98.
 17. Mandal M, Tripathy R, Panda AK, Pattanaik SS, Dakua S, Pradhan AK, et al. Vitamin D levels in Indian systemic lupus erythematosus patients: association with disease activity index and interferon alpha. *Arthritis Res Ther*. 2014; 16: R49.
 18. Kamen DL, Cooper GS, Bouali H, Shaftman SR, Hollis BW, Gilkeson GS. Vitamin D deficiency in systemic lupus erythematosus. *Autoimmun Rev*. 2006; 5: 114-117.
 19. Cutolo M, Otsa K. Review: vitamin D, immunity and lupus. *Lupus*. 2008; 17: 6-10.
 20. Niewold TB, Clark DN, Salloum R, Poole BD. Interferon alpha in systemic lupus erythematosus. *J Biomed Biotechnol*. 2010; 2010: 948364.
 21. Heshmat R, Mohammad K, Majdzadesh SR, Forouzanfar MH, Bahrami A, Ranjbaromarani GH, et al. Vitamin d deficiency in Iran: A Multi-center study among different urban areas. *Iranian J Public Health*. 2008; 37: 72-78.
 22. Saedinea A, Larijani B, Jalaline S, Farzadfar F, Keshtkar F, Rezae A, et al. Evaluation of prevalence deficiency of vitamin D in Iranian population the province during 1990-2010. *Iran J Diabetes Metab*. 2013; 12: 574-584.
 23. Hashemipour S, Larijani B, Adibi H, Javadi E, Sedaghat M, Pajouhi M, et al. Vitamin D deficiency and causative factors in the population of Tehran. *BMC Public Health*. 2004; 4: 38.
 24. Sumethkul K, Boonyaratavej S, Kitumnaypong T, Angthararuk S, Cheewasat P, Manadee N, et al. The predictive factors of low serum 25-hydroxyvitamin D and vitamin D deficiency in patients with systemic lupus erythematosus. *Rheumatol Int*. 2013; 33: 1461-1467.
 25. Toloza SM, Cole DE, Gladman DD, Ibañez D, Urowitz MB. Vitamin D insufficiency in a large female SLE cohort. *Lupus*. 2010; 19: 13-19.
 26. Ruiz-Irastorza G, Egurbide MV, Olivares N, Martinez-Berriotxo A, Aguirre C. Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. *Rheumatology*. 2008; 47: 920-923.
 27. Gholamrezaei A, Bonakdar ZS, Mirbagher L, Hosseini N. Sleep disorders in systemic lupus erythematosus. Does vitamin D play a role? *Lupus*. 2014; 23: 1054-1058.
 28. Kimball SM, Mirhosseini N, Rucklidge J. Database Analysis of Depression and Anxiety in a Community Sample-Response to a Micronutrient Intervention. *Nutrients*. 2018; 10: 152.
 29. Zhang L, Fu T, Yin R, Zhang Q, Shen B. Prevalence of depression and anxiety in systemic lupus erythematosus: a systematic review and meta-analysis. *BMC Psychiatry*. 2017; 17: 70.
 30. Sotodeh-Asl N, Tamadon MR, Malek F, Zahmatkesh M. Vitamin D deficiency and psychological disorders. *J Parathyroid Dis*. 2014; 2: 21-25.