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Assessment of serum vitamin D level and its relationship with disease activity in adult patients with Systemic Lupus Erythematosus (SLE)

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Vitamin D level varies according to the geographic location. This study was conducted to evaluate Vitamin D level in the serum samples of Systemic lupus erythematosus (SLE) patients from Iranian population and determine its association with SLE disease activity index (SLEDAI), sun exposure, smoking, photosensitivity, sun protector cream use, and drug regimen. In this cross-sectional study, 200 patients were included. The patient's data were obtained using a questionnaire. The enzyme-linked immunosorbent assay (ELISA) technique was used to determine Vitamin D level in the serum samples of the patients. The study population was comprised of 27 (13.5%) males and 173 (86.5%) females, with the mean age of 38.46 ± 13.24 years. Serum level of Vitamin D was 13.62 ± 3.22 ng/ml in the patients. Vitamin D deficiency was observed in 104 (52%) patients. There was a statistically positive correlation between vitamin D level and duration of sun exposure (CC = 0.57, $P = 0.004$). A statistically significant negative correlation was seen between vitamin D level and SLEDAI (CC = -0.41, $P = 0.013$). Vitamin D level was significantly ($P = 0.030$) lower in the SLE patients with photosensitivity. SLE patients using sun protector cream had significantly ($P = 0.002$) lower level of Vitamin D. Patients receiving glucocorticoid drugs had significantly ($P = 0.001$) lower levels of Vitamin D in comparison to the patients not receiving glucocorticoids. Vitamin D is involved in the disease activity of SLE patients. It is important to include vitamin D supplementation in drug regimen of SLE patients, especially when it includes glucocorticoids.

Keywords: Vitamin D; Systemic lupus erythematosus; photosensitivity; disease activity; glucocorticoids

Introduction

Vitamin D is a steroid hormone that has a critical role in calcium metabolism, skeletal health, immune system regulation, and bone homeostasis [1]. Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are two physiological forms of vitamin D [2]. The principal origin of vitamin D3 is assembly by the conversion of 7-dehydrocholesterol to pre-vitamin D3 in the skin by UVB rays-exposed surface, and a smaller amount of it is provided by the diet [3]. Recently, an epidemic of vitamin D deficiency has been demonstrated and numerous studies have shown a relationship between vitamin D insufficiency and several autoimmune and inflammatory diseases [4, 5]. Vitamin D receptor (VDR) is located on several immune cells and mediate immunomodulatory functions by downstream signaling. Several investigations have demonstrated that vitamin D participates in the regulation of the immune responses by inhibiting T helper 1 (Th1), Th17 , and B cells and by promoting the development of Th2 and regulatory T (Treg) cells [6, 7].

Systemic lupus erythematosus (SLE) is the paradigm of multisystemic autoimmune disorders characterized by cellular and humoral immunological irregularities, leading to the secretion of pathogenic autoantibodies [8]. Numerous studies have been proposed that vitamin D has a crucial role in the development and pathogenesis of SLE based on the results and observations of clinical and laboratory investigations [9, 10]. Evidence has shown that vitamin D induces downregulation of the Th1 and activates B cells immune response while upregulating Treg cells during SLE pathogenesis [11-13]. Various risk factors for vitamin D deficiency have been shown in SLE Patients. The photosensitivity feature of SLE prepares lower sun

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appearance and the use of sunscreen, which prevents ultraviolet B (UVB) transmission, decreasing the skin generation of vitamin D [14]. Also, renal impairment, which can happen in subjects with lupus nephritis, could break the hydroxylation of vitamin D [15]. Above all, chronic use of immunosuppressive drugs (especially corticosteroid) as well as medications used regularly for SLE therapy change the metabolism of vitamin D [16].

As physiological and clinical consequences of vitamin D deficiency in SLE are not entirely known, this study was designed to assess vitamin D level in the serum of these patients and its association with disease activity.

Materials and Methods

Patients

In this cross-sectional study, 200 Iranian patients with SLE were included. The following simple formula was used for calculating the adequate sample size in our study; $n = Z^2 P (1-P) / d^2$

Where n is the sample size, Z is the statistic corresponding to the level of confidence, P is expected prevalence (that can be obtained from same studies or a pilot study conducted by the researchers), and d is precision (corresponding to effect size). Simple random sampling was employed for random selection. In cross-sectional studies, the aim is to estimate the prevalence of unknown parameter(s) from the target population using a random sample. The outpatient visits were performed in the Rheumatology Clinic of the Ali-Ebne-Abitaleb Hospital of Rafsanjan, Kerman, Iran, between May and November 2019. SLE patients were diagnosed according to the American College of Rheumatology (ACR) criteria in 1997 [17]. Patients with other connective tissue diseases, and pregnantand lactating subjects were eliminated from the study. The demographic data are illustrated in Table 1. The disease activity was defined on the day the serum samples were drawn using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score [18]. The study was confirmed by the Human Research Ethics Committee of Rafsanjan University of Medical Sciences and written informed consent was obtained from all subjects (1398.103).

Table 1. Patients characteristics.

Patient characteristics	n (%) or Mean ± SD
Gender (Male/Female)	27 (13.5%) / 173 (86.5%)
Age (years, Mean ± SD)	38.46 ± 13.24
Age at SLE diagnosis (years, Mean ± SD)	26.44± 7.25
Disease duration (years, Mean ± SD)	12.74 ± 6.87
SLEDAI (Mean ± SD)	5.74 ± 3.21
Sun exposure (hrs/day Mean ± SD)	1.28 ± 0.15
Vitamin D level (ng/ml, Mean ± SD)	13.62 ± 3.22
Vitamin D deficiency	104 (52%)
Smoking	14 (7%)
Malar rash	112 (56%)
Discoid rash	24 (12%)
Mucosal lesion	86 (43%)
Arthritis	146 (73%)
Pleuritis	27 (12.5)
Proteinuria	11 (5.5%)
Hematuria	76 (38%)
Urine casts	29 (14.5%)
Renal involvement	26 (13%)
Anemia	62 (31%)
Hypertension	35 (17.5%)
Pericarditis	20 (10%)
Cardiomyopathy	3 (1.5%)

Patient characteristics	n (%) or Mean ± SD
Leukopenia	75 (37.5%)
Lymphopenia	64 (32%)
Thrombocytopenia	42 (21%)
Photosensitivity	122 (61%)
Vitamin D supplementation	70 (35%)
Immunosuppressive use	64 (32%)
Glucocorticoid use	124 (62%)
Antimalarial use	197 (98.5%)
Prednisolone use	32 (16%)
Sun protector cream use	88 (44%)

SLE; Systemic lupus erythematosus, SLEDAI; Systemic lupus erythematosus disease activity index, SD; Standard deviation

Measurement of 25(OH) D3 level and definition of insufficiency

To evaluate vitamin D levels, 5 ml of peripheral blood samples were obtained from all study subjects. After that, serum samples were isolated from the whole bloods and stored in the -80 °C refrigerator until further evaluations. Vitamin D levels were analyzed by Enzyme-linked immunosorbent assay (ELISA) technique using a commercial kit (CALBIOTECH, CA, USA).

In this study, we applied the widely used cut-off points for describing Vitamin D deficiency, insufficiency and sufficiency as suggested previously by Munns et al. [19]. Therefore, a Vitamin D level less than 12 ng/ml (< 30 nmol/L) was recognized as Vitamin D deficiency, a level between 12-20 ng/ml (30-50 nmol/L) was considered Vitamin D insufficiently, and an optimal level (sufficiency) was determined to be more than 20 ng/ml (50 nmol/L).

Statistical Analysis

SPSS version 22.0 for Windows program (SPSS Inc., Chicago, IL, USA) was utilized for statistical analyses. The normality of the data was ensured through Kolmogorov–Smirnov test. Mann-Whitney U test was run to compare the clinical data between the two groups, and Spearman's rho correlation test was applied to analyze correlations. Missing data were also considered during statistical analysis. Additionally, the univariate and multivariate regression analyses were carried out to adjust the association between serum vitamin D level and SLEDAI for confounding factors. A P-value of less than 0.05 was regarded to be statistically significant.

Results

Demographic information and clinicopathological presentations

The demographic information and clinicopathological presentations of the study subjects are listed in Table 1. The study population was comprised of 27 (13.5%) males and 173 (86.5%) females, with the mean age of 38.46 ± 13.24 years. The mean age of subjects at SLE diagnosis was 26.44 ± 7.25 years, and the disease duration of the patients was 12.74 ± 6.87 years. The mean SLEDAI of the patients was 5.74 ± 3.21. The mean sun exposure of the patients was detected at 1.28 ± 0.15 hrs/day. Among the patients, 88 (44%) individuals were using sun protector cream on a daily basis. Vitamin D supplements were consumed by 70 (35%) patients.

Vitamin D level and determination of insufficiency

It was detected that serum level of Vitamin D was 13.62 ± 3.22 ng/ml in the patients. According to the criteria described above, it was observed that 104 (52%) patients were suffering from Vitamin D deficiency.

Correlation of Vitamin D level with patients' data

The correlation of Vitamin D level with numerical characteristics of SLE patients are shown in Table 2. No statistically significant correlation was detected between the Vitamin D level and age [correlation co-efficient (CC) = -0.12, p value = 0.245], at SLE diagnosis (CC = -0.26, p value = 0.112), and disease duration (CC = -0.29, p value = 0.088). There was a statistically positive correlation between vitamin D level in the serum of patients and duration of sun exposure (CC = 0.57, p value = 0.004). However, a statistically significant negative correlation was seen between vitamin D level in the serum of patients and SLEDAI (CC = -0.41, p value = 0.013).

Table 2. Correlation of Vitamin D level with numerical characteristics of SLE patients.

Patient characteristics	Correlation co-efficient	P value
Age	-0.12	0.245
Age at SLE diagnosis	-0.26	0.112
Disease duration	-0.29	0.088
Sun exposure	0.57	0.004
SLEDAI	-0.41	0.013

SLE; Systemic lupus erythematosus, SLEDAI; Systemic lupus erythematosus disease activity index

Association of Vitamin D level with patient's data

Association of Vitamin D level with nominal characteristics of SLE patients are presented in Table 3. Although Vitamin D level was higher in female SLE patients (12.32 ± 2.14 ng/ml) in comparison to the males (14.92 ± 3.48 ng/ml), it was not significantly different between male and female patients (*p value* = 0.146). In addition, no significant difference (*p value* = 0.188) was detected between smoker (12.42 ± 3.09 ng/ml) and non-smoker SLE patients (14.82 ± 3.38 ng/ml).

Vitamin D level was significantly (*p value* = 0.030) lower in SLE patients with photosensitivity (11.29 ± 2.01 ng/ml) compared with the patients without photosensitivity (15.95 ± 4.43 ng/ml). Moreover, SLE patients using sun protector cream (10.21 ± 2.10 ng/ml) had significantly (*p value* = 0.002) lower level of Vitamin D in comparison to the patients who did not use sun protector cream (17.03 ± 4.34 ng/ml). Nonetheless, Vitamin D level was not significantly different between patients having or lacking other clinicopathological presentations, including malar rash, discoid rash, mucosal lesion, arthritis, pleuritis, proteinuria, hematuria, urine casts, renal involvement, anemia, hypertension, pericarditis, cardiomyopathy, leukopenia, lymphopenia and thrombocytopenia.

Finally, in spite of lower levels of vitamin D in patients consuming immunosuppressive (*p value* = 0.074), antimalarial (*p value* = 0.903), and prednisolone drugs (*p value* = 0.362), the differences were not statistically significant. However, patients receiving glucocorticoid drugs, had significantly (*p value* = 0.001) lower levels of Vitamin D in comparison to the patients who were not taking glucocorticoids (Table 3).

Table 3. Association of Vitamin D level with nominal characteristics of SLE patients.

Patient characteristics	Present	Absent	P value
Gender (Male/Female)	Male: 12.32 ± 2.14	Female:14.92 ± 3.48	0.146
Smoking	12.42 ± 3.09	14.82 ± 3.38	0.188
Malar rash	12.11 ± 2.85	15.13 ± 3.59	0.065
Discoid rash	12.55 ± 3.20	14.69 ± 3.24	0.244
Mucosal lesion	13.18 ± 2.47	14.06 ± 3.97	0.198
Arthritis	12.99 ± 2.76	14.25 ± 3.68	0.324
Pleuritis	12.56 ± 2.45	14.68 ± 3.99	0.087
Proteinuria	12.77 ± 3.12	14.47 ± 3.32	0.136
Hematuria	13.19 ± 3.14	14.05 ± 3.30	0.236
Urine casts	12.89 ± 3.18	14.35 ± 3.26	0.258
Renal involvement	12.50 ± 3.17	14.74 ± 3.27	0.144
Anemia	12.26 ± 2.74	14.98 ± 3.70	0.378
Hypertension	12.39 ± 2.80	14.85 ± 3.64	0.366
Pericarditis	13.14 ± 3.09	14.10 ± 3.35	0.281
Cardiomyopathy	13.25 ± 3.12	13.99 ± 3.32	0.367
Leukopenia	13.08 ± 2.95	14.16 ± 3.49	0.464
Lymphopenia	13.13 ± 3.20	14.11 ± 3.24	0.380

Patient characteristics	Present	Absent	*P value*
Thrombocytopenia	12.87 ± 2.76	14.37 ± 3.68	0.233
Photosensitivity	11.29 ± 2.01	15.95 ± 4.43	0.030
Immunosuppressive use	12.22 ± 2.65	15.02 ± 3.79	0.074
Glucocorticoid use	09.17 ± 2.19	18.07 ± 4.25	0.001
Antimalarial use	13.54 ± 3.10	13.70 ± 3.34	0.903
Prednisolone use	13.46 ± 3.07	13.78 ± 3.37	0.762
Sun protector cream use	10.21 ± 2.10	17.03 ± 4.34	0.002

Regression analysis

Univariate regression analysis revealed no association between serum vitamin D level and SLEDAI upon adjusting for the confounding factors, such as smoking status and sun protector cream use. Additionally, multivariate regression analysis indicated no association between serum vitamin D level and the disease activity after adjusting for the confounding factors, including disease duration and sun exposure (Table 4).

Table 4. Univariate and multivariate regression analyses of the association between serum vitamin D level and the disease activity (SLEDAI).

	Univariate regression			Multivariate regression		
	Z-score	*P* value	OR (95% CI)	Z-score	*P value*	OR (95% CI)
Smoking	-1.234	0.126	0.65 (0.48-1.253)	-0.742	0.367	0.75 (0.61-1.49)
Sun protector cream use	-0.385	0.700	0.864 (0.41-1.81)	-0.769	0.442	0.69 (0.28-1.75)
Disease duration (Year)	-	-	-	0.240	0.084	1.06 (0.78-1.65)
Sun exposure (hrs/day)	-	-	-	0.121	0.822	1.08 (0.56-2.32)

Discussion

In this study, we tried to evaluate the association of vitamin D level with different indexes in the SLE patients, among which age in particular, gender distribution, SLEDAI, sun exposure, smoking, photosensitivity, sun protector cream use, and drug regimen. Most importantly, we found that Vitamin D level had significantly negative and positive correlation with SLEDAI and duration of sun exposure, respectively. Moreover, Vitamin D level was lower in patients with photosensitivity and those using sun protector cream. In addition, patients taking glucocorticoid drugs, had lower levels of Vitamin D when compared to those not consuming glucocorticoids.

Widely distributed around the world, SLE has an unknown etiology as well as clinical and laboratory manifestations in different races and regions [20]. It can occur at any age, including childhood, but it is most common in the second, third or fourth decade of life. Although the disease is found in both sexes, it is far more common in women. The disease is also more common in people of African and Hispanic origin [21]. According to an extensice sociological study of rheumatic disease, the prevalence of SLE in Iran has been estimated to be 40 per 100,000 [22].

In 2019, Ospina-Caicedo *et al*. conducted a cross-sectional study where the 25-OH Vitamin D level was evaluated in 69 SLE patients above 18 years of age. It was found that 36.2% of patients had low levels of vitamin D with higher levels of anti-dsDNA. SLE patients with moderate to severe disease activity had lower values of Vitamin D based on SLEDAI. The Vitamin D level was higher in patients who did not consume steroids than the patients receiving 0.5-1mg/kg/d dosage of steroids [23]. We found inverse correlation of Vitamin D level and SLEDAI. Furthermore, patients receiving glucocorticoid drugs had lower levels of Vitamin D in comparison to those who did not. As a consequence, it is critical to monitor Vitamin D level in SLE patients regularly and include Vitamin D supplementation in their medication regimen, particularly when glucocorticoids are included in their drug administrations.

Vitamin D level has been shown to impress several immune system pathways, which in turn imposes remarkable consequences for patients with SLE [24]. SLE patients have several risk factors for Vitamin D deficiency. Photosensitivity, which is a specific manifestation of SLE patients, might reduce sunlight exposure time, which decelerates the production of Vitamin D through the skin. Long-term corticosteroids consumption and other immunosuppressive drugs in lupus patients also affects

Vitamin D metabolism. On the other hand, renal involvement in nephritic patients with lupus can impact hydroxylation and activation of Vitamin D [25]. Our study revealed that Vitamin D level was significantly lower in SLE patients with photosensitivity compared to the patients lacking photosensitivity. In addition, 44% of patients were using sun protector cream, who had significantly lower level of Vitamin D in comparison to those not using sun protector creams. Furthermore, Vitamin D level had a positive correlation with daily duration of sun exposure. Interestingly, we detected a negative correlation between Vitamin D level and SLE disease activity. Therefore, it seems that lower sunlight absorption (even though 35% patients were taking Vitamin D supplementation) caused Vitamin D deficiency in the SLE patients , which may exacerbate clinical manifestations. Hence, it is suggested that SLE patients.

Considering that vitamin D level had positive correlation with sun exposure duration but a negative correlation with SLEDAI, it might be beneficial for the patients to have at least one hour of daily sun exposure to decrease the disease activity. In addition, physicians are highly recommended to prescribe Vitamin D to the SLE patients to regulate the disease activity and improve the general mood of the patents. Additionally, it might be beneficial for the patients to use less of the sun protector creams, which may increase sunlight absorption by skin and Vitamin D production consequently. Our study had some limitations. Firstly, the small sample size may have influenced the serum 25-(OH)D levels. Accordingly, it could be speculated that the low levels of 25-(OH)D in the SLE patients in our study might stem from the sample size, meaning that they were not the source of the disease activity. Secondly, there were no healthy controls with whom to compare the prevalence of VitD insufficiency and deficiency. Finally, in our study, it was impossible to determine anti-dsDNA, C3, C4, or other serum markers in all of the patients.

Conclusion

Taking all the evidence together, this study revealed that Vitamin D level was negatively and positively correlated with SLEDAI and duration of sun exposure, respectively, in the SLE patients. Moreover, Vitamin D level was lower in patients with photosensitivity and those using sun protector cream. Besides, SLE patients receiving glucocorticoid drugs, had lower levels of Vitamin D in comparison to those who did not. Therefore, it is recommended for the physicians to include Vitamin D supplementation in their medication prescriptions for SLE patients, particularly when glucocorticoids are already being consumed. Furthermore, it would be advantageous for the patients to be exposed to sunlight provided that there is no photosensitivity.

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Conflict of interest

Noun.

References

1. Carmeliet G, Dermauw V, Bouillon R. Vitamin D signaling in calcium and bone homeostasis: a delicate balance. *Best Pract Res Clin Endocrinol Metab* 2015; 29(4):621-31. doi: 10.1016/j.beem.2015.06.001.

2. Romagnoli E, Mascia ML, Cipriani C, Fassino V, Mazzei F, D'Erasmo E. *et al*. Short and long-term variations in serum calciotropic hormones after a single very large dose of ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) in the elderly. *J Clin Endocrinol Metab* 2008; 93(8):3015-20. doi: 10.1210/jc.2008-0350.

3. Maurya VK, Aggarwal M. Factors influencing the absorption of vitamin D in GIT: an overview. *J food sci technol* 2017; 54(12):3753-65. doi: 10.1007/s13197-017-2840-0.

4. Yin K, Agrawal DK. Vitamin D and inflammatory diseases. *J Inflamm Res* 2014; 7:69-87. doi: 10.2147/JIR.S63898

5. Kamen DL, Tangpricha V. Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity. *J Mol Med (Berl)* 2010; 88(5):441-50. doi: 10.1007/s00109-010-0590-9.

6. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. *Curr Opin Pharmacol* 2010; 10(4):482-96. doi: 10.1016/j.coph.2010.04.001.

7. Ikeda U, Wakita D, Ohkuri T, Chamoto K, Kitamura H, Iwakura Y. *et al*. 1α, 25-Dihydroxyvitamin D3 and all-trans retinoic acid synergistically inhibit the differentiation and expansion of Th17 cells. *Immunol Lett* 2010; 134(1):7-16. doi: 10.1016/j.imlet.2010.07.002.

8. Choi J, Kim ST, Craft J. The pathogenesis of systemic lupus erythematosus—an update. *Curr Opin Immunol* 2012; 24(6):651-57. doi: 10.1016/j.coi.2012.10.004.

9. 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(12):CR711-18. doi: 10.12659/msm.882131.

10. Kamen DL, Aranow C. The link between vitamin D deficiency and systemic lupus erythematosus. *Curr Rheumatol Rep* 2008; 10(4):273-80. doi: 10.1007/s11926-008-0044-3.

11. Guillot X, Semerano L, Saidenberg-Kermanac'h N, Falgarone G, Boissier M-C. Vitamin D and inflammation. *Joint Bone Spine* 2010; 77(6):552-57. doi: 10.1016/j.jbspin.2010.09.018.

12. Chambers ES, Hawrylowicz CM. The impact of vitamin D on regulatory T cells. *Curr Allergy Asthma Rep* 2011; 11(1):29-36. doi: 10.1007/s11882-010-0161-8.

13. Sheikh V, Kasapoglu P, Zamani A, Basiri Z, Tahamoli-Roudsari A, Alahgholi-Hajibehzad M. Vitamin D3 inhibits the proliferation of T helper cells, downregulate CD4+ T cell cytokines and upregulate inhibitory markers. *Hum Immunol* 2018; 79(6):439-45. doi: 10.1016/j.humimm.2018.03.001.

14. De Haven C. Vitamin D Status And Sunscreen Use. 2014.

15. Nerviani A, Mauro D, Gilio M, Grembiale RD, Lewis MJ. To Supplement or not to Supplement? The Rationale of Vitamin D Supplementation in Systemic Lupus Erythematosus. *Open Rheumatol J* 2018; 12(1):226-47. doi.org/10.2174/1874312901812010226.

16. Gröber U, Kisters K. Influence of drugs on vitamin D and calcium metabolism. *Dermato-endocrinol* 2012; 4(2):158-66. doi: 10.4161/derm.20731.

17. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40(9):1725-25. doi: 10.1002/art.1780400928.

18. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002; 29(2):288-91.

19. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K. *et al.* Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. *J Clin Endocrinol Metab* 2016; 101(2):394-15. doi: 10.1210/jc.2015-2175.

20. Lau C, Yin G, Mok M. Ethnic and geographical differences in systemic lupus erythematosus: an overview. *Lupus* 2006; 15(11):715-19. doi: 10.1177/0961203306072311.

21. Paolino S, Smith V, Pizzorni C, Seriolo B, Sulli A, Cutolo M: **Vitamin D, autoimmune diseases, and systemic lupus erythematosus**. In: *Connective Tissue Disease.* Springer; 2016: 159-68.

22. Moghimi N, Davatchi F, Rahimi E, Saidi A, Rashadmanesh N, Moghimi S. *et al.* WHO-ILAR COPCORD study (stage 1, urban study) in Sanandaj, Iran. *Clin Rheumatol* 2015; 34(3):535-43. doi: 10.1007/s10067-013-2430-0.

23. Ospina-Caicedo AI, Cardona-Rincón AD, Bello-Gualtero JM, Valle-Oñate R, Romero-Sánchez C, Chalem-Choueka P. *et al.* Lower levels of vitamin D associated with disease activity in Colombian patients with systemic lupus erythematosus. *Curr Rheumatol Rev* 2019; 15(2):146-53. doi: 10.2174/1573397114666181015161547.

24. Ahearn JM, Liu C-C, Kao AH, Manzi S. Biomarkers for systemic lupus erythematosus. *Transl Res* 2012; 159(4):326-42. doi: 10.1016/j.trsl.2012.01.021.

25. Winters SJ. Systemic Lupus Erythematosus and Vitamin D: Should We Recommend That Our Patients Take Supplements? *Am J Med Sci* 2019; 358(2):93-94. doi: 10.1016/j.amjms.2019.05.009.