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ORIGINAL ARTICLE

Association of vitamin D deficiency and disease activity in systemic lupus erythematosus patients: Two-year follow-up study

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ABSTRACT

Objectives: This study aims to determine the prevalence of vitamin D deficiency in Pakistani systemic lupus erythematosus (SLE) patients and the effect of vitamin D deficiency on the severity and outcomes of SLE.

Patients and methods: This retrospective study evaluated SLE patients presenting to our hospital between January 2009 and December 2018. A total of 98 patients (13 males, 85 females; mean age 39.8±14.9 years; range, 16 to 73 years) with vitamin D levels available at the time of diagnosis were included in the study. Disease activity was measured using SLE disease activity score at the time of diagnosis and at the two-year mark.

Results: Sixty-five patients were deficient in Vitamin D and out of those 46 were severely deficient. The severe disease group had more patients with vitamin D deficiency at both visits (43/78 and 33/46) while patients in remission all had normal vitamin D (12/12 and 14/14) ($p \leq 0.001$).

Conclusion: Vitamin D deficiency is common in SLE patients and also significantly associated with increased disease activity at the time of diagnosis and at the two-year mark. We hope this study becomes a platform for the global medical community to come together and implement early screening and monitoring of vitamin D levels and to determine the optimal level of supplementation for prevention of poor outcomes in SLE.

Keywords: Autoimmune disease, rheumatology, systemic lupus erythematosus, vitamin D.

Vitamin D is the common denomination of a collection of sterols belonging to a class of secosteroids playing a vital role in phosphocalcic metabolism. The main circulating form of vitamin D is 25-hydroxy vitamin D (25-(OH)D) formed by hydroxylation of cholecalciferol in the liver.[1,2] Its function is mediated through the vitamin D receptors (VDRs) which are not only found in bones and kidney but also in muscles.[1] Immune cells including the dendritic cells, macrophages, monocytes, and lymphocytes (B and T cells) are capable of converting 25-(OH)D3 to 1,25-(OH)2D3, theoretically endowing the immunocytes with a higher level of vitamin D-related immune response control at the inflamed sites and demonstrating the important role that vitamin D has in the immune system.[2] Another piece of evidence that suggests a potential role of vitamin D in the immune system and the mediation of autoimmune diseases is the presence of VDR polymorphisms, namely, ApaI, FokI, BsmI, and TaqI, which have been found to be associated with the development of autoimmunity.[2,3]

Systemic lupus erythematosus (SLE) is a multisystem autoimmune inflammatory disease mainly affecting females of childbearing age. It is characterized by a large spectrum of clinical

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manifestations accompanied by prototypic abnormalities of the immune system characterized by immune-complex induced inflammation.[4]

One of the most effective ways of assessing severity of this disease is by continuously monitoring disease activity which also helps in determining prognosis and extent of organ damage, ultimately dictating the treatment modality. The SLE Disease Activity Index 2000 (SLEDAI-2K) has been the most widely used SLE disease activity measure.[5] However, the performance of SLEDAI in detecting clinically meaningful changes in disease activity is limited, since each item of SLEDAI is scored dichotomically, with the same numerical weight regardless of the severity of change observed.[6] In addition, potentially severe lupus manifestations, such as hemolytic anemia, pneumonitis, types of rash, and systemic vasculitis are not scored in SLEDAI.[6]

These limitations had important implications on target-driven management of SLE in daily clinical practice, and in assessing the efficacy of new medications in clinical trials. Thus, there was an urgent need for a new tool which was able to accurately capture clinically meaningful changes in SLE disease activity. Jesus et al.,[6] validated a new tool for the measurement of SLE disease activity: the SLE disease activity score (SLE-DAS). This provides an accurate, continuous, and user-friendly global measure of SLE disease activity with improved sensitivity to change and high specificity, in comparison to SLEDAI-2K.

Systemic lupus erythematosus patients are at a heightened risk of being deficient in vitamin D due to reduced exposure to the sun, renal damage, and continuous use of medications (such as chronic steroids and hydroxychloroquine) with the potential of altering metabolism of vitamin D.[7] SLE has been found to be substantially T-cell driven with the T helper type 1 (Th1) and Th17 cluster of differentiation 4+ T cells being chiefly responsible for driving the pro-inflammatory response in SLE.[8] As 1,25-(OH)2D3 dampens the pro-inflammatory response of Th17, it is theoretically possible to suppress the SLE disease with vitamin D treatment.

Studies from around the world have stated the prevalence of vitamin D deficiency in SLE patients to be varied but up to 90% in some articles.[1,9] Unfortunately, there is scarcity of local data to look for vitamin D status in autoimmune diseases. Only two articles were found that show the relationship of vitamin D with rheumatoid arthritis and vitiligo in Pakistani population;[10,11] however, to our knowledge, no study has been conducted investigating the association of SLE and vitamin D in Pakistani population. Therefore, in this study, we aimed to determine the prevalence of vitamin D deficiency in Pakistani SLE patients and the effect of vitamin D deficiency on the severity and outcomes of SLE.

PATIENTS AND METHODS

This retrospective study was conducted at Department of Medicine, Aga Khan University Hospital. A total of 500 patients were diagnosed as SLE during hospital stay or clinic appointment between January 2009 and December 2018. Diagnosis of SLE was confirmed by applying the Systemic Lupus International Collaborating Clinics-12 criteria.[12] This visit was characterized as the first visit (even if the patient had disease previously or had been newly diagnosed) to the hospital and vitamin D levels were noted from this visit. The second visit of the patient was taken after 48 months and disease activity was assessed at both visits and then compared with relation to vitamin D level. Patients with vitamin D not checked within one week of the first visit or those who were already on vitamin D supplements, or had other existing connective tissue diseases, hepatitis B, hepatitis C, human immunodeficiency virus, sarcoidosis, parathyroid disorders, chronic liver disease, or chronic kidney disease were excluded. Finally, 98 patients (13 males, 85 females; mean age: 39.8±14.9 years; range, 16 to 73 years) were included. The study protocol was approved by the Ethical Review Committee of the Aga Khan University Hospital. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The data were collected from the medical records of patients using a pre-designed pro forma. Information collected included demographics, clinical characteristics of SLE, vitamin D levels, and SLE-DAS at the time of diagnosis and at the two-year mark. Disease activity was also

monitored via complement component (C) 3, C4, and anti-double-stranded deoxyribonucleic acid (anti-dsDNA). Anti-dsDNA was labeled as positive with values of greater than 25 IU/mL while C3 and C4 values of less than 0.8 and 0.1 were considered as significant. Vitamin D levels were categorized as normal (more than 20 ng/mL), mild deficiency (less than 20 ng/mL), and severe deficiency (less than 12 ng/mL). SLE-DAS was used to calculate DAS at both visits and then on the basis of the score, the disease was appropriately categorized as remission (less than 2.08), low disease activity (less than 3.77), moderate disease activity (less than 7.64), and severe disease activity (more than 7.64).[6]

Statistical analysis

The IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Qualitative variables were presented as frequency and percentages and continuous variables as mean with standard deviation. For continuous variables, we used Student t-test or Wilcoxon rank-sum test and chi-square test or Fisher exact test for categorical variables to identify differences between the vitamin D deficient and non-deficient groups. P value less than 0.05 was considered statistically significant.

RESULTS

Among the included patients, 87% were females and the mean age at the time of diagnosis was 39.8±14.9 years (range, 16 to 73 years). The most common clinical manifestations were mucosal ulcers

Table 1. Comparison of demographics and clinical characteristics of systemic lupus erythematosus patients according to level of vitamin D deficiency

		Level of vitamin D deficiency			
	Overall (n=98)	Normal vitamin D level (n=33)	Mild vitamin D deficiency (n=29)	Severe vitamin D deficiency (n=46)	
	n	n	n	n	*p*
Age (year)					0.809
<45	64	23	12	29	
>45	34	10	7	17	
Sex					0.593
Male	13	6	2	5	
Female	85	27	17	41	
Residence					0.963
Urban	67	22	13	32	
Rural	31	11	6	14	
Arthritis	51	15	12	24	0.469
Localized rash	44	14	11	19	0.445
Generalized rash	24	8	3	13	0.568
Alopecia	21	7	1	13	0.121
Mucosal ulcers	56	16	10	30	0.302
Systemic vasculitis	25	6	6	13	0.476
Mucocutaneous vasculitis	21	8	2	11	0.435
Neuropsychiatric symptoms	12	1	1	10	0.026
Serositis	20	4	1	15	0.016
Cardiopulmonary features	23	3	3	17	0.011
Myositis	19	2	2	15	0.007
Proteinuria	29	9	2	18	0.067
Leukopenia	15	3	5	7	0.252
Hemolytic anemia	31	4	5	22	0.001
Thrombocytopenia	31	3	6	22	0.003

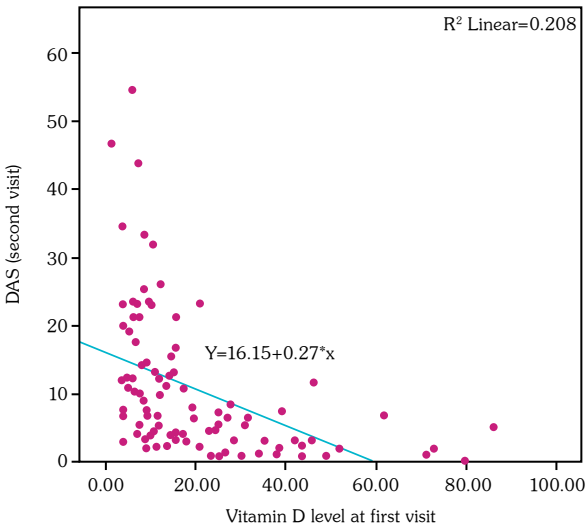

Figure 1. Scatter plot showing inverse relationship between vitamin D levels and systemic lupus erythematosus disease activity scores at end of study period (48 months after first visit).
DAS: Disease activity score.

(n=56; 57%), arthritis (n=51; 52%), and localized rash (n=44; 452%). Mean vitamin D level was 19.9±17.8 (range, 1.5 to 85.9). Sixty-five patients were deficient in Vitamin D and out of those 46 were severely deficient. Table 1 compares the clinical characteristics of SLE with vitamin D level status. Severe vitamin D deficiency was significantly associated with neuropsychiatric symptoms, serositis, cardiopulmonary features, myositis, hemolytic anemia, and thrombocytopenia (p≤0.05).

The overall mean SLE-DASs at diagnosis and at the two-year mark were 30.9±19.0 (range, 0 to 80) and 10.9±10.4 (range, 0 to 54), respectively. Figure 1 illustrates the inverse relationship between the vitamin D levels and the SLE-DASs. Table 2 shows the comparison between vitamin D levels and SLE disease activity indicators. C3 and C4 levels showed a significant association with vitamin D levels (p≤0.05). Furthermore, there was a significant association between SLE-DAS status and vitamin D deficiency. The severe disease group had more patients with vitamin D deficiency at both visits (43/78 and 33/46) while patients in remission all had normal vitamin D (12/12 and 14/14) (p≤0.001).

DISCUSSION

The role of vitamin D and the impact of its deficiency on multiple autoimmune diseases have long been a subject of discussion in the medical literature. SLE patients have a complicated relationship with vitamin D. The reason behind this is because some researchers believe that

Table 2. Comparison of systemic lupus erythematosus disease activity indicators according to level of vitamin D deficiency

	Overall (n=98)	Level of vitamin D deficiency			
		Normal vitamin D level (n=33)	Mild vitamin D deficiency (n=29)	Severe vitamin D deficiency (n=46)	
	n	n	n	n	*p*
ANA	62	17	12	33	0.184
Anti-dsDNA	68	19	14	35	0.192
Decreased C3 and C4	41	8	11	22	0.032
SLE-DAS (first visit)					0.001
Severe	78	17	18	18	
Moderate	6	2	1	1	
Mild	2	2	0	0	
Remission	12	12	0	0	
SLE-DAS (second visit)					0.001
Severe	46	3	10	33	
Moderate	26	10	6	10	
Mild	12	6	3	3	
Remission	14	14	0	0	

ANA: Antinuclear antibody; Anti-dsDNA: Anti-double-stranded deoxyribonucleic acid antibody; C3 and C4: Complement components 3 and 4; SLE-DAS: Systemic lupus erythematosus-disease activity score.

SLE patients have multiple risk factors resulting in vitamin D deficiency, while the rest are of the opinion that vitamin D deficiency is itself a cause of SLE in such patients.[9]

The results of this study have demonstrated that vitamin D deficiency is an extremely common occurrence in SLE patients with two thirds being deficient and more than half being severely deficient. It has also showed that there is a strong association between vitamin D deficiency and disease activity. Other studies have displayed a similar level of prevalence which ranges from 16 to 96% and can vary depending on a number of factors such as environmental, geographical, and genetic factors.[13]

The mean vitamin D level in the present study was 19.8±17.8 ng/mL, which is almost similar to that seen in Egypt (17.6±6.9 ng/mL), Saudi Arabia (19.1±9.5 ng/mL), and Spain (22 ng/mL).[1,9,14] In contrast, an Indian study reported very low mean vitamin D level of around 11.61.[15] However, prevalence of vitamin D deficiency in the present study was around 64.3% which is quite lower than all four studies above which have mentioned a prevalence of greater than 90% in each. As this is a retrospective study, this might be due to the poor data record.

There are few studies evaluating the association of vitamin D deficiency and SLE disease activity and even fewer assessing long-term outcomes. Our study demonstrates an inverse relationship between vitamin D levels and SLE disease activity. Patients with vitamin D deficiency had a significantly higher disease activity at the time of diagnosis and two years later. A recent report by Amital et al.[16] displayed similar results using the SLEDAI and European Consensus Lupus Activity Measurement scoring systems, and presented an inverse correlation between the two variables. Similarly, Ben-Zvi et al.[17] also reported an increasing trend of disease activity with decreasing vitamin D levels. Dutta et al.,[18] in their very recent study from India, concluded that the vitamin D deficient group was three times more likely of developing high disease activity (odds ratio: 3.9; $p<0.05$) compared with the control group.

This study has some limitations. The findings of the study are limited due to a retrospective study design, small sample size because of fewer patients having recorded Vitamin D levels and due to the use of a new scale for assessing disease severity which has not been used at a big scale. Furthermore, since the majority of the patients presenting to our tertiary hospital had either been previously admitted elsewhere or were from far-flung areas, true vitamin D values could not be found. Another problem with retrospective data collection was the quality of the data in the file and the variability in the examinations performed by physicians. Still, this study is the first of its kind from Pakistan which assesses the prevalence of vitamin D deficiency in SLE patients and also demonstrates the association between vitamin D deficiency and SLE disease activity. It offers new local information to clinicians which can influence clinical practice. However, to better understand the impact of vitamin D deficiency on SLE patients and to assess its prognostic significance, further specifically designed prospective cohort studies are needed.

In conclusion, vitamin D deficiency is prevalent in SLE patients and is significantly associated with more active disease at the time of diagnosis and at the two-year mark. We hope this study becomes a platform for the global medical community to come together and implement early screening and monitoring of vitamin D levels and to determine the optimal level of supplementation for prevention of poor outcomes in SLE.

Declaration of conflicting interests

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