ORIGINAL ARTICLE

Vitamin D Levels and Steroid Usage are not Associated with Disease Activity in Systemic Lupus Erythematosus Patients

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ABSTRACT

Introduction: Suboptimal vitamin D levels are commonly presented by systemic lupus erythemathosus (SLE) patients. This is likely due to protection measures from sunshine exposure adopted by SLE patients to reduce the likelihood of SLE flares onset. In this study, we investigated the vitamin D level among SLE patients and its association with SLE Disease Activity (SLEDAI) scores and among groups of steroid and non-steroid usage. **Methods:** We recruited 84 SLE patients who attended the Rheumatology Clinic of Hospital Universiti Sains Malaysia from June 2018 until October 2018. Their clinico-demographic data were retrieved and serum vitamin D immunoassay was conducted to measure the vitamin D levels of each patient Vitamin D levels were categorized as normal (≥75nmol/L), insufficient (50-74 nmol/L) or deficient (<50 nmol/L). Comparison between the clinico-demographic parameters with vitamin D levels were conducted using the Fisher's exact test (for categorical variables) and unpaired t-test (for continuous variables). **Results:** The mean vitamin D level among the subjects was 40.79 ± 20.2 nmol/L. Fifty-eight (69%) patients were vitamin D deficient, while 20 (23.8%) patients were vitamin D insufficient, and only 6 (7.1%) patients had sufficient level of vitamin D. Vitamin D status was not significantly associated with SLEDAI score (p=0.185) as well as between steroids and non-steroids groups (p=0.255). **Conclusion:** Vitamin D deficiency occurred in majority of our SLE patients. SLE disease activities were not associated with the status of vitamin D or steroid usage.

Keywords: Systemic lupus erythematosus, SLEDAI score, Vitamin D, Steroids

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic, multifactorial and chronic autoimmune disease with characteristic deregulated levels of autoantibodies and multiple distinct secreted factors.(1-5) SLE is heterogeneous in its presentation that involves multiple organs and organ damage that is irreversible is a major outcome of concern in these patients. (6-8) This includes the onset of osteoporosis and bone loss that represent major causes of irreparable injury in SLE patients. (9-10)

Vitamin D plays pivotal roles in the metabolism of calcium and hence bone homeostasis. In the liver, vitamin D is metabolized into 25-hydroxyvitamin D, the form clinically measured in serum immunoassays for vitamin D status. Vitamin D is further metabolized into 1,25-dihydroxyvitamin D in the kidney. 1,25-dihydroxyvitamin D is capable of binding to the vitamin D receptor (VDR), a type of nuclear receptor expressed by multiple types of immune cells such as antigen-presenting cells, B and T cells. Hence, vitamin D is capable of regulating immune responses, and deregulated vitamin D levels are involved in the immunopathogenesis of autoimmune disorders. (11-12)

Vitamin D deficiency occurs in several autoimmune diseases such as SLE. Vitamin D deficiency is a risk factor for the onset and development of disease activity in SLE. (13) Apart from risks of bone disease and fractures, muscle weakness, fatiguability, increased risks of cardiovascular and renal disease are all known complications of vitamin D deficiency in SLE.(14). Inadequate vitamin D levels have been reported in numerous SLE cohorts in different geographic locations and at various periods of the year. (15-18) This study was conducted given the paucity of data on vitamin D

status among Malaysian SLE patients.

MATERIALS AND METHODS

Recruitment of SLE patients

A total of 84 SLE patients who attended the Rheumatology Clinic in Hospital Universiti Sains Malaysia in Kelantan, Malaysia, were recruited in this study. Patients above 18 years old who fulfilled at least four criteria of the American College of Rheumatology Classification criteria for SLE, or renal biopsy consistent with lupus nephritis (LN), were considered eligible for inclusion in this study.(19) Post-menopausal at time of diagnosis, pregnancy and lactating women, chronic liver and kidney disease, chronic gastrointestinal upset (more than 3 months of loose stool or diarrhea), small bowel resection and gastric were excluded from the study. The disease activities of SLE were measured by the SLE Activity Index (SLEDAI). SLEDAI measures the lupus disease activity of a patient in the past 10 days, and SLEDAI includes 24 weighted clinical and laboratory items. SLEDAI score ranges from 0 to 105, and score ≥6 indicates active disease while <6 indicates inactive disease. (20-22)

The clinico-demographic characteristics of the patients were retrieved from the unit records and the status of disease activity was assessed based on their symptoms. The data collected and examined were as follows:

(1) Demographical data: Age, gender, and duration of the disease.

(2) Clinical data: Clinical manifestations of SLE including cutaneous lesions, arthritis, hematological, lupus nephritis and neuropsychiatric symptoms, steroid dosage and duration of steroid usage, administration of calcium and vitamin D supplement, duration of sunlight exposure and sunscreen usage. The disease activity was measured by the SLEDAI score.

(3) Laboratory results: Serum levels of vitamin D.

Serum vitamin D immunoassay

Serum vitamin D concentration was measured by chemiluminescence immunoassay on an automated analyzer (UniCel Dxl 800, Beckman Coulter Inc., USA). Serum vitamin D was defined as deficient when the level was <50 nmol/L and insufficient when it was 50-74 nmol/L. Serum vitamin D concentration ≥75nmol/L was considered adequate.

Statistical analysis

For univariate analysis, two groups of patients with or without active disease were produced. Differences between categorical variables were analyzed by Fisher's exact test, and unpaired t-test was used to analyze differences between continuous variables. For all analyses, categorical variables were presented as number and percentage, and continuous variables were presented as mean and standard deviation (SD). Vitamin D was categorized as normal (≥75nmol/L), insufficient (50-74 nmol/L) or deficient (<50 nmol/L). All analyses were performed using SPSS v24 (SPSS Inc., Chicago, IL, USA). For all tests, two-tailed $p<0.05$ was considered statistically significant.

Ethical clearance

This study was reviewed and approved by the Human Research Ethics Committee, Universiti Sains Malaysia (approval registration number: USM/JEPeM/18040213).

RESULTS

Clinico-demographical characteristics

In this study, a total of 84 patients were included (Table I). Majority of the patients were female (92.3%; n=78/84) while 7.1% (n=6/84) were male. The mean age of the patients was 36.04 ± 10.09 years (mean ± SD) ranging from 18 to 50 years old. The average disease duration was 7.4 ± 7.77 years with mean duration of steroid usage was 5.51 ± 5.47 years. A total of 66.7% (n=56/84) of the patients were on steroid for the past 30 days while 33.3% (n=28/84) were not on steroid due to disease remission. The mean dose of steroid was 6.71 ± 8.66 mg.

The average SLEDAI score at vitamin D level measurement was 1.33 ± 2.76 points (Table I). A total of 21.4% (n=18/84) had active disease (SLEDAI score

Table I: Clinico-demographic characteristics of the SLE patients (n=84)

Variable		n (%)
Age (Mean [SD])		36.04 (10.09)
Sex	Female	78 (92.9%)
	Male	6 (7.1%)
Duration of SLE (Mean [SD])		7.40 (7.77)
Disease activity	Active	18 (21.4%)
	Inactive	66 (78.6%)
SLEDAI score (Mean [SD])		1.33 (2.76)
Mucocutaneous	Yes	60 (71.4%)
	No	24 (28.6%)
Arthritis	Yes	42 (50%)
	No	42 (50%)
Hematological	Yes	27 (32.1%)
	No	57 (67.9%)
Renal	Yes	23 (27.4%)
	No	61 (72.6%)
CNS	Yes	7 (8.3%)
	No	77 (91.7%)
Steroid	Yes	56 (66.7%)
	No	28 (33.3%)
Duration of steroid (Mean [SD])		5.51 (5.47)
Mean dose of steroid (Mean [SD])		6.71 (8.66)

>4) at the time of vitamin D measurement while 78.6% (n=66/84) had inactive disease (SLEDAI score <4). Mucocutaneous (71.4%; n=60/84) and arthritis (50%; n=42/84) were the most common clinical manifestations of SLE while hematological manifestations were documented in 32.1% (n=27/84), LN in 27.4% (n=23/84) and neuropsychiatry symptoms in 8.3% (n=7/84) of SLE patients.

Distribution of vitamin D status in SLE patients

Table II shows the descriptive statistics of vitamin D levels among all participants. Mean level of vitamin D was 40.79 ± 20.20 nmol/L (Table II). Majority of the SLE patients (n=58/84; 69%) presented with vitamin D deficiency, while 20 (23.8%) patients were vitamin D insufficient, and only 6 (7.1%) patients had sufficient levels of vitamin D.

Comparison between vitamin D levels and the disease activity in SLE patients

In SLE patients who were vitamin D-deficient (n=58), 46 (79.3%) of the patients had inactive disease, while the remaining 12 (20.7%) patients had active disease (Table III).

Table II: Vitamin D characteristics and factors influencing vitamin D levels in SLE patients (n=84)

Variable		n (%)
Vitamin D supplement	Yes	65 (77.4%)
	No	19 (22.6%)
Calcium supplement	Yes	65 (77.4%)
	No	19 (22.6%)
Sunscreen usage	Never	27 (32.1%)
	Occasional	35 (41.7%)
	Always	22 (26.2%)
Daily sunlight exposure	<15 minutes	69 (82.1%)
	≥15 minutes	15 (17.9%)
Vitamin D (Mean [SD])		40.79 (20.20)
Vitamin D	Deficient	58 (69%)
	Insufficient	20 (23.8%)
	Sufficient	6 (7.1%)

Among vitamin D insufficient group (n=20), 17 (85%) of the patients had inactive disease, and the remaining 3 (15%) patients had active disease. For vitamin D sufficient group (n=6), equivalent numbers were observed between inactive and active disease activity. No association was observed between vitamin D levels and SLE disease activity (p=0.185). Comparison of vitamin D levels with SLE disease activity also did not yield significance difference (p=0.631) (Table IV).

Comparison between steroid usage and the levels of vitamin D in SLE patients

Overall, 56 (66.7%) SLE patients were on steroid for the past 30 days with mean steroid dosage of 6.71 ± 8.66 mg (Table IV). Among steroid users, 37 (44%) patients had deficient vitamin D level, 13 (15.5%) patients had insufficient amount and 6 (7.1%) patients had sufficient level of vitamin D.

Compared with non-steroid users, vitamin D deficiency was observed among 21 (25%) patients, while 7 (8.3%) were vitamin D insufficient. None of the patient who were non-steroid users had sufficient vitamin D level. The difference of vitamin D level in both groups was insignificant (p=0.255).

DISCUSSION

Majority of the SLE patients were female with average age of the patients was 36.04 ± 10.09, ranging from 18 to 50 years old and comparable with previous studies where majority of SLE patients were middle-aged women. (13,24) Mean vitamin D levels in our patients' cohort was 40.79 ± 20.2 nmol/L which is lower compared with previous Malaysian studies by Yeap et al. (23) and Ong et al. (24) who reported higher mean vitamin D levels (51.3 ± 11.5 and 54.3 ± 14.8 nmol/L, respectively).

Despite Malaysia being a tropical country, prevalence of vitamin D deficiency among Malaysian adolescents was relatively high (33%).(25) Our study demonstrated that the prevalence of vitamin D deficiency and insufficiency among Malaysian SLE patients was expectedly higher, at 92.8%. A previous study on an independent cohort

Table III: Comparison of vitamin D status with SLE disease activity or steroid usage (n=84)

Deficient		Vitamin D			*p*-value
		Insufficient	Sufficient		
SLE disease activity	Inactive	46 (54%)	17 (20.2%)	3 (3.6%)	0.185
	Active	12 (14.3%)	3 (3.6%)	3 (3.6%)	
Steroid	Yes	37 (44%)	13 (15.5%)	6 (7.1%)	0.255
	No	21 (25%)	7 (8.3%)	0 (0%)	

Table IV: Comparison of vitamin D levels with disease activity (n=83)

Variable	Inactive disease, mean (SD)	Active disease, mean (SD)	MD (95% CI)	T statistic (df)	*p*-value
Vitamin D	40.23 (17.73)	42.83 (28.02)	-2.6 (-13.33, 8.13)	-0.482 (82)	0.631

of Malaysia SLE patients reported the prevalence to be 78.7%, (24) hence we concluded that vitamin D deficiency and insufficiency in Malaysian SLE patients ranges from 78-93%. Other studies have reported lower prevalence of vitamin D deficiency and insufficiency in their SLE cohort of patients including the multi-centre study by Letratanakul et al. (26) that described the prevalence at 72.3%, and involved patients from Europe, North America and Asia. Studies conducted by Souto et al.(27) in Brazil and Yap et al.(28) in Australia reported prevalence of 45.9% and 27.7%, respectively. (27,28) Nevertheless, studies conducted in China, Egypt, Hong Kong, Mexico and Spain reported prevalence of suboptimal vitamin D levels that exceeded 90% or greater (29-31) similar with our observations.

SLE patients have multiple risk factors for vitamin D deficiency. One of the common factors is lower sun exposure as sunlight can cause SLE flares (photosensitivity rash). Hence, SLE patients tend to stay indoors and apply sunscreen to protect their skin from sunlight that can lead to decreased vitamin D production in the skin. (32) Our study demonstrated that 69 (82.1%) patients had sun exposure at less than 15 minutes with approximately 70% of the patients applied sunscreen for sunlight protection, suggesting that their lower levels of vitamin D was attributable to decreased exposure to sunlight. Previous studies have reported the association between suboptimal vitamin D level and photosensitivity. (29,33) was reported by Ruiz-Irastorza et al. (29) and Kamen et al.(33) Nevertheless, other studies Gao et al.,(30) Garcia-Carrasco et al.(34) and Souto et al.(27) reported insignificant correlation between suboptimal vitamin D levels and photosensitivity among Chinese, Brazilian and Mexican SLE patients, respectively. (27, 30, 34)

Other factors include involvement of LN leading to decreased 1 α-hydroxylase activity, causing impaired synthesis of 1,25-dihydroxyvitamin D, the active form of vitamin D. Drugs such as steroids and hydroxychloroquine also enhance vitamin D metabolism, and autoantibodies against vitamin D contribute to its clearance. (35-36) Our study showed that vitamin D deficiency was not associated with active SLE. Absence of their association was also reported by other studies in populations from different nations, and lower vitamin D level did not predict disease flare up.(37)

Nonetheless, multiple other studies have reported the association of lower vitamin D levels with SLE disease activity as follows: (1) Borba et al. demonstrated that Brazilian premenopausal SLE patients (n=36) with a high SLEDAI score had lower average vitamin D levels compared with patients with a low SLEDAI score;(38) (2) Yeap et al. observed that Vitamin D deficiency or insufficiency presented with worse SLE disease activity, and an increase in serum vitamin D over time was associated with reduced disease activity;(23) (3) In a study involving 378 European SLE patients, Amital et al. reported that Lower vitamin D levels were associated with patients with active disease in a study involving 378 European SLE patients .(39)

Furthermore, we did not observe any association between steroid usage and levels of vitamin D. This finding is comparable with other reports where association between vitamin D and glucocorticoid (21) or corticosteroid use. (34) Nonetheless, Amy et al. showed that steroid use in SLE patients (n=181) was independently associated with vitamin D deficiency. (32) In our study, most of the patients received lower steroid dose with mean steroid dosage of 6.71 ± 8.66 mg, and this might contribute to the insignificant association between vitamin D levels and steroid usage.

CONCLUSION

In conclusion, vitamin D levels is not associated with and steroid usage and are not associated with SLE disease activity. As this study only involved SLE patients, it would be beneficial for future studies to include age and sex matched healthy controls groups. We recommend that future, multicenter studies involving larger numbers of cases in Malaysia are required to confirm the observations in our study of Malaysian SLE patients.

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