Original Article

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Vitamin D status and its relationship with systemic lupus erythematosus as a determinant and outcome of disease activity

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Abstract:

Background: The importance of vitamin D (VD) in systemic lupus erythematosus (SLE) is being increasingly appreciated, with studies suggesting a relationship between VD deficiency and SLE onset/disease activity. We investigated VD status in SLE patients and its associations with disease activity in a geographical region of India receiving low solar ultraviolet-B (UV-B) index.

Materials and methods: We enrolled 109 SLE patients along with 109 healthy controls belonging to same ethnicity and localities. Demographic and clinico-laboratory information were recorded. VD status was assessed by estimating serum 25-hydroxyvitamin D (25-OH-D) concentrations (deficient: <20 ng/mL, insufficient: 21–29 ng/mL, and sufficient/normal: ≥30 ng/mL) using an enzyme-linked fluorescent assay (ELFA). The SLE Disease Activity Index (SLEDAI) scoring system was used to evaluate disease activity. The association between VD status and disease activity was assessed by univariate and multivariate approaches.

Results: Hypovitaminosis D was prevalent in 90.83% SLE patients [vs. 77.98% healthy controls; chi-squared (χ^2) = 10.125, df = 2, p < 0.01]. SLEDAI scores and 25-OH-D values were inversely associated, which extended in a two-way manner as revealed by multiple logistic regression models. SLE patients with VD deficiency were more likely to have high/very high disease activity [adjusted odds ratio (OR) = 3.5, 95% confidence intervals (CI): 1.4–8.9]. Conversely, patients with high SLEDAI scores (>10) also had greater risks of being VD deficient (adjusted OR = 3.9, 95% CI: 1.5–10.8).

Conclusion: VD deficiency is widespread in SLE. The relationship appears to be bidirectional, with VD status associated both as determinant and outcome of disease activity in SLE.

Keywords: 25-hydroxyvitamin D, disease activity, risk factor, systemic lupus erythematosus, vitamin D deficiency

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disorder of the connective tissues that may involve multiple organ systems in the body. The susceptibility to SLE is determined by both genetic and environmental factors. The clinical course of SLE is variable ranging from mild to severe; and the presentations are diverse, which may drastically differ even within the same patient over time [1], [2], [3]. Assessment of disease activity in SLE is critical as it helps in evaluating disease severity, chronic damage and prognosis of the patient, and thereby guides treatment decisions. Besides, longitudinal assessment of disease activity in an SLE patient is useful for identifying flare ups and evaluating response to therapy and remission [4], [5], [6].

Vitamin D is an endogenously synthesized steroid hormone traditionally known for its role in calcium homeostasis and bone metabolism. However, vitamin D is now being increasingly recognized as a potent immunomodulator that regulates both innate and adaptive immune responses [7], [8]. Recent studies have implicated vitamin D deficiency in the pathogenesis and clinical course of several autoimmune disorders, including

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SLE [9]. Deficiency of vitamin D has been previously documented in SLE patients [10], [11], [12], [13], [14]. Animal model experiments as well as clinical studies have suggested that vitamin D status is critical as it could determine the clinical course, severity and disease activity in SLE [15], [16], [17], [18], [19], [20], [21], [22]. However, it is also believed that disease activity in SLE influences the vitamin D status in the body.

Cutaneous exposure to solar ultraviolet B (UV-B) irradiation converts the precursor molecule 7-dehydrocholesterol to cholecalciferol, which in turn is transformed to 25-hydroxyvitamin D (25-OH-D) in the liver and further to the physiologically active form 1,25-dihydroxyvitamin D (or calcitriol) in the kidney. Vitamin D deficiency is widespread in the general population of India and the northeastern region especially receives a low UV-B index as compared to the other parts of the country [23]. But, a review of the existing literature reveals that there is a scarcity of information on the status of vitamin D and its significance in SLE patients from India in general and from the northeast in particular. Previous studies on SLE from the northeastern region have documented a variety of clinico-laboratory presentations [24], [25], [26], [27], some often distinct from elsewhere in the country [24], [26]. The current study was conceived with the aim of investigating vitamin D status and its association with SLE in patients from northeast India. Further, the relationship of vitamin D status with disease severity and clinical manifestations of SLE was also evaluated.

Materials and methods

Study design and sample size

A hospital-based analytical cross-sectional study was conducted, involving two groups of subjects, namely (i) a case group (consisting of SLE patients), and (ii) a control group (consisting of healthy individuals) in a tertiary care teaching hospital at Dibrugarh, Assam in the northeastern region of India.

The study was powered at 85% with a two-sided $\alpha = 0.05$. The prevalence of vitamin D deficiency in the general population was considered as 70% based upon previous data [28], and it was conservatively expected to detect an odds ratio (OR) of at least 3. Based upon these assumptions, it was found that at least 99 individuals would be needed for each group if the cases and controls were to be selected at a 1:1 ratio according to Kelsey's method. On the other hand, as per Fleiss' method with continuity correction, using the same assumptions, the number of individuals required in each group was found to be 108. These sample size calculations were performed using OpenEpi v3.0.1 (http://www.OpenEpi.com).

Study participants and data collection

On the basis of the above sample size estimations, 109 patients with SLE (diagnosed as per 1997 – revised American College of Rheumatology criteria) [29], were recruited prospectively for the case group between July 2014 and June 2015 from the Rheumatology out-patient department (OPD). The exclusion criteria were pregnancy or lactation, co-presence of other autoimmune disorders, liver disease, parathyroid disorders, osteomalacia, calcium supplementation, vitamin D supplementation and using substances or drugs that may interfere with fat absorption. The disease activity of SLE was assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scoring system [30]. Accordingly, the disease activity was classified as follows: no activity (score 0), mild activity (score 1–5), moderate activity (score 6–10), high activity (score 11–19) or very high activity (score ≥20). During the same visit, the status of vitamin D was determined by measurement of serum 25-OH-D concentrations as per Endocrine Society Clinical Practice Guidelines (CPG) (deficient: <20 ng/mL, insufficient: 21–29 ng/mL and sufficient: ≥30 ng/mL) [31]. These measurements were done by enzyme-linked fluorescent assay (ELFA) technique in a mini-Vidas® analyzer (BioMerieux SA, Marcy l'Étoile, France). Quantitative estimation of anti-dsDNA was performed by a commercially available anti-dsDNA indirect solid phase enzyme-linked immunosorbent assay (ELISA) IgG kit (HYCOR Biomedical, Garden Grove, CA, USA).

For comparison of vitamin D status, 109 healthy individuals (who were in sound health, and without history of autoimmune disorders, hepatic or renal disorder) from similar socio-economic backgrounds and from the same ethnicity and geographical areas were also enrolled in the control group for the study during the same period.

Statistical analysis

The data were analyzed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). Continuous data were presented as mean [with standard deviation (SD)] or median (with range) depending upon whether they were normally

distributed or not (tested by the Kolmogorov-Smirnov test). Subsequently, their comparison among groups were performed by an unpaired t-test, the Mann-Whitney U test, one-sided analysis of variance (ANOVA) or the Kruskal-Wallis test, as appropriate. On the other hand, the categorical data were expressed as count (with percentage), and their comparisons were performed by Fisher's exact test or the chi-square (χ^2)-test, as appropriate. The association between vitamin D status and SLE was assessed by calculating the OR and 95% confidence interval (CI). The association of vitamin D deficiency (as a predictor variable) with SLE disease activity (as a dependent variable) was also assessed through crude OR and 95% CI estimates after dichotomizing the 25-OH-D levels (<20 ng/mL vs. ≥20 ng/mL) and SLEDAI scores (>10 vs. ≤10). The independent association was further verified by estimating the adjusted OR (with corresponding 95% CI) using multiple logistic regression after controlling for covariates, namely history of photosensitivity (yes or no), disease duration, whether newly diagnosed (or known case), serum anti-dsDNA levels, age, and treatment with hydroxychloroquine (yes or no) and treatment with steroid (yes or no). In an additional set of analyses, vitamin D status was included as a dependent/outcome variable to calculate adjusted OR (with 95% CI) for determining the predictors of vitamin D deficiency. The predictor variable considered in these analyses were SLEDAI scores (high or not, i.e. SLEDAI > 10 vs. ≤10). The diagnosis type (i.e. newly diagnosed or known case), age, disease duration, serum anti-dsDNA levels, renal involvement (yes or no), photosensitivity (yes or no), hydroxychloroquine use (yes or no), and steroid use (yes or no) were the other covariates included in these analyses. Further, calendar month (sample collection and 25-OH-D estimation) was also considered as a covariate to account for the seasonal variation in 25-OH-D levels during these analyses. In all calculations, a two-tailed p-value < 0.05 was regarded as statistically significant.

Ethics

The study complied with the tenets of the Helsinki Declaration and it was approved by the Institutional Ethics Committee. Voluntary informed written consent was procured from all the participants of the study.

Results

The case group consisted of 109 SLE patients (age = 25.8 ± 8.5 years) of which only three were males. Overall, 80 patients were previously diagnosed known cases of SLE, of which 16 patients were non-compliant to treatment; whereas 29 patients were newly diagnosed. The median duration of disease was 24 months (range = 0–324 months). Clinically, nephritis was the commonest clinical presentation (~80%). Other frequent manifestations were mucocutaneous (~73%), musculoskeletal (~49%), hematological (~54%) and constitutional (~77%) in nature (Table 1). Median SLEDAI score was 12 (range = 0–68), with the majority of the patients (~34%) classified as having high disease activity (SLEDAI = 11–19). On the other hand, eight patients (7.3%) showed no disease activity (SLEDAI = 0). Anti-dsDNA values ranged from 4.3 to 877 IU/mL (median = 102 IU/mL), while ESR values ranged from 3 to 150 mm (median = 40 mm).

Table 1: Characteristics of the systemic lupus erythematosus (SLE) cases and healthy controls.

Variable	Case group (n = 109)	Control group (n = 109)	p-Value
Age, years	25.8 ± 8.5	25.2 ± 6.6	0.55
Sex			
Male	3 (2.75)	5 (4.59)	0.72
Female	106 (97.25)	104 (95.41)	
Vitamin D status			
Normal, 25-OH-D ≥ 30 ng/mL	10 (9.17)	24 (22.02)	$p < 0.01$ ($\chi^2 = 10.1$, $df = 2$)
Insufficient, 25-OH-D < 30 ng/mL	38 (34.87)	44 (40.37)	$p_{trend} < 0.01$
Deficient, 25-OH-D < 20 ng/mL	61 (55.96)	41 (37.61)	($\chi^2_{trend} = 10.1$, $df = 1$)
25-OH-D, ng/mL	20.2 ± 9.5	23.4 ± 8.7	<0.05
Anti-dsDNA, IU/mL	102 (4.3–877)	–	–
ESR (mm AEFH)	40 (3–150)	–	–
Clinical profile			
Nephritis	87 (79.8)	–	–
Musculoskeletal (arthritis, myositis)	53 (48.6)	–	–

Vasculitis	9 (8.3)	–	–
Serositis (pleurisy, pericarditis)	22 (20.2)	–	–
Mucocutaneous (photosensitivity, malar rash, alopecia, mucosal ulcers, etc.)	80 (73.4)	–	–
Constitutional (fever, malaise, anorexia fatigue, etc.)	84 (77.1)	–	–
Hematological (anemia, thrombocytopenia, leucopenia)	59 (54.1)	–	–
CNS manifestations (seizures, psychosis, headache, etc.)	10 (9.2)	–	–
SLEDAI score	12 (0–68)	–	–
SLEDAI scorewise disease activity categories			
0 (no activity)	8 (7.3)	–	–
1–5 (mild activity)	16 (14.7)	–	–
6–10 (moderate activity)	23 (21.1)	–	–
11–19 (high activity)	37 (34)	–	–
≥20 (very high)	25 (22.9)	–	–
Medication use			
Hydroxychloroquine	51 (46.8)	–	–
Steroid	54 (49.5)	–	–
Mycophenolate mofetil	16 (14.7)	–	–
Azathioprine	9 (8.3)	–	–
Cyclophosphamide	6 (5.5)	–	–

CNS, central nervous system; 25-OH-D, 25-hydroxyvitamin D; ESR, erythrocyte sedimentation rate; AEFH, at end of 1st hour; SLEDAI, SLE disease activity index; *df*, degree of freedom.
The continuous data are expressed as mean ± standard deviation or median (minimum value–maximum value). Categorical data are expressed as count (%).

The patients in the case group were comparable to subjects in the control group (n = 109) with respect to age (p = 0.55) and sex (p = 0.72) composition (Table 1). Subjects in both the groups were non-vegetarian (meat, fish, eggs) with respect to dietary habits. A significantly greater proportion of SLE subjects had inadequate vitamin D status as opposed to the healthy controls (χ^2 = 10.1, *df* = 2, p < 0.01). This pattern was also reflected by the mean serum 25-OH-D levels, which were significantly lower (p < 0.05) in the SLE case group (20.2 ± 9.5 ng/mL) than in the healthy control group (23.4 ± 8.7 ng/mL). While normal vitamin D status was observed in nearly 22% of the healthy controls, only about 9% of the SLE patients had normal vitamin D status. Vitamin D deficiency (i.e. 25-OH-D levels < 20 ng/mL) was found to be significantly associated with SLE (OR = 2.7, 95% CI = 1.5–4.7, p < 0.01 when compared with individuals with 25-OH-D levels ≥ 20 ng/mL; and OR = 3.6, 95% CI = 1.6–8.3, p < 0.01 when compared with individuals with 25-OH-D ≥ 30 ng/mL) (Supplementary Table 1).

The SLEDAI scores varied significantly across different vitamin D categories (KW statistic = 9.5, p < 0.01) (Table 2), such that SLE patients with vitamin D deficiency exhibited the highest SLEDAI scores (median = 14, range = 0–38), followed by the ones who had vitamin D insufficiency (median = 10, range = 0–68) and then by the ones who had normal vitamin D status (median = 7, range = 0–24). In fact, the SLE patients who were deficient in vitamin D (i.e. serum 25-OH-D < 20 ng/mL) had more than 3 times higher odds (p < 0.05) of developing high disease activity (OR = 3.9, 95% CI = 1.3–11.7) or very high disease activity (OR = 3.5, 95% CI = 1.1–11.5) as compared to SLE patients who had serum 25-OH-D levels ≥ 20 ng/mL (Supplementary Table 2). This independent association between vitamin D deficiency (25-OH-D < 20 ng/mL) and high/very high SLE disease activity (i.e. SLEDAI scores > 10) persisted in a statistically significant manner (adjusted OR = 3.5, 95% CI = 1.4–8.9, p < 0.01) even after accounting for covariates (Table 3). In addition, a history of photosensitivity enhanced the risk for high/very high disease activity (adjusted OR = 2.2, 95% CI = 0.9–5.5), whereas hydroxychloroquine (HCQ) treatment was protective against developing high/very high disease activity (adjusted OR = 0.5, 95% CI = 0.1–3.4), although statistically these associations were non-significant (corresponding p-values 0.1 and 0.48).

Table 2: Comparison of SLEDAI scores, anti-dsDNA and ESR values across vitamin D status categories.

Variables	Vitamin D status (serum 25-OH-D levels)			KW statistic (corrected for ties)	p-Value
	Normal, (>30 ng/mL	Insufficient, 20–29 ng/mL	Deficient, <20 ng/mL		
SLEDAI score	7 (0–24)	10 (0–68)	14 (0–38)	9.5	<0.01
Anti-dsDNA	78.6 (4–267)	76.5 (6–877)	110 (13.6–440)	2.7	0.26

ESR	34 (5–150)	41 (3–144)	40 (4–145)	0.5	0.79

SLEDAI, systemic lupus erythematosus disease activity index; ESR, erythrocyte sedimentation rate; 25-OH-D, 25-hydroxyvitamin D; KW statistic, Kruskal-Wallis statistic.
The values are expressed as median (minimum value–maximum value).

Table 3: Predictors of high/very high SLE disease activity (SLEDAI score > 10) by multiple logistic regression.

Variable	Adjusted OR	95% CI	p-Value (Wald test)
Age, years	0.9	0.9–1.1	0.98
Vitamin D deficiency, 25-OH-D < 20 ng/mL	**3.5**	**1.4–8.9**	<0.01
Newly diagnosed SLE	0.4	0.1–1.5	0.19
Disease duration, months	0.9	0.8–1.02	0.13
Photosensitivity	2.2	0.9–5.5	0.10
Hydroxychloroquine treatment	0.5	0.1–3.4	0.48
Steroid treatment	1.3	0.2–8.9	0.79
Serum anti-dsDNA levels, IU/mL	1.0	0.9–1.01	0.12

SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; 25-OH-D, 25-hydroxyvitamin D; OR, odds ratio; CI, confidence interval.
The statistically significant associations are highlighted in bold.

Within the SLE patients in our study, the 25-OH-D values varied in a significant manner ($p < 0.05$) between the patients with and without photosensitivity (17.8 ± 7.9 ng/mL and 21.7 ± 10.1 ng/mL, respectively) (Table 4). However, the concentrations of 25-OH-D in the SLE patients did not vary significantly as a function of hydroxychloroquine use ($p = 0.18$) or steroid use ($p = 0.22$) or presence of nephritis ($p = 0.15$) or whether they were newly diagnosed or not ($p = 0.22$). Comparisons of 25-OH-D levels according to the clinical involvement are shown in Supplementary Table 3.

Table 4: Comparison of 25-OH-D concentrations across different sub-groups of SLE patients.

Variables	25-OH-D levels (ng/mL) across different sub-groups of SLE patients		p-Value
	Yes	No	
Newly diagnosed SLE	18.3 ± 8.5	20.9 ± 9.8	0.22
Photosensitivity	17.8 ± 7.9	21.7 ± 10.1	<0.05
Nephritis	19.5 ± 9.1	22.8 ± 10.9	0.15
Hydroxychloroquine use	21.5 ± 10.8	19.0 ± 8.1	0.18
Steroid use	21.3 ± 10.5	19.1 ± 8.3	0.22

SLE, systemic lupus erythematosus; 25-OH-D, 25-hydroxyvitamin D.
The 25-OH-D values are expressed as mean ± SD.

Moreover, the 25-OH-D levels in the SLE patients differed significantly across the SLEDAI score categories (KW statistic = 10.6, $p < 0.05$) (Supplementary Table 4). The patients having the lowest category of disease activity had the highest median 25-OH-D concentrations (median = 24.8 ng/mL, range = 12.8–68 ng/mL), whereas the patients with the highest disease activity category displayed the least median 25-OH-D concentrations (median = 17.5 ng/mL, range = 8.2–31.7 ng/mL). When the predictors of vitamin D deficiency in SLE were assessed by multiple logistic regression (Table 5), it was observed that high/very high disease activity (i.e. SLEDAI > 10) (adjusted OR = 3.9, 95% CI = 1.5–10.8, $p < 0.01$) continued to be an independent risk factor, in addition to disease duration (adjusted OR = 1.2, 95% CI = 1.04–1.4, $p < 0.05$). Further, newly diagnosed SLE patients were protected (adjusted OR = 0.2, 95% CI = 0.1–0.8, $p < 0.05$) against vitamin D deficiency as compared to known SLE patients. The presence of photosensitivity also appeared to be a risk factor (adjusted OR = 1.8, 95% CI = 0.7–4.3) for vitamin D deficiency, but the association was statistically not significant ($p = 0.23$).

Table 5: Predictors of vitamin D deficiency (25-OH-D < 20 ng/mL) in SLE patients assessed by multiple logistic regression.

Variable	Adjusted OR	95% CI	p-Value (Wald test)

Age, years	1.003	0.9–1.1	0.98
High SLE disease activity (SLEDAI score > 10)	**3.9**	**1.5–10.8**	<0.01
Nephritis	1.3	0.4–4.1	0.67
Newly diagnosed SLE	**0.2**	**0.1–0.8**	<0.05
Disease duration, months	**1.2**	**1.0–1.4**	<0.05
Photosensitivity	1.8	0.7–4.3	0.23
Hydroxychloroquine treatment	1.6	0.3–9.8	0.62
Steroid treatment	1.1	0.2–7.2	0.89
Serum anti-sDNA levels, IU/mL	1	0.9–1.003	0.94

SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; 25-OH-D, 25-hydroxyvitamin D; OR, odds ratio; CI, confidence interval.
The statistically significant associations are highlighted in bold.

Discussion

The role of vitamin D as an environmental trigger for SLE and modulator of disease severity is of much interest. SLE is a complex multisystem disorder with debilitating complications. As vitamin D is a naturally occurring ubiquitous substance – its major source being dermal conversion of 7-dehydrocholesterol under UV light exposure, therefore it offers the attractive prospect of regulating the pathogenesis and clinical course of the disease by maintaining adequate levels in the body. Indians in general are known to have a high preponderance of hypovitaminosis D [32]. Vitamin D status varies with ethnicity and geography. Northeast India represents an ethnological transition zone, such that its population has similarities to other Indian populations, but with discernible Mongoloid elements relatable to neighboring Myanmar, Thailand and China [33]. Geographically, the region is situated between two major subcontinental regions, namely the Indian subcontinent to the west and the East/Southeast Asia region to the east. A recent multi-centric study from India had documented that the UV-B index (essential for synthesis of vitamin D) is the least in the northeastern region [23]. Dibrugarh in Upper Assam is located in northeast India (at 27.48°N and 94.91°E coordinates). The status of vitamin D in SLE in this region and its role in influencing the disease activity was investigated for the first time in this study. Although vitamin D deficiency/insufficiency was prevalent in both the SLE patients and healthy controls in the current study, yet the SLE patients had significantly lower 25-OH-D concentrations and a higher prevalence of hypovitaminosis D than the healthy controls. As per the CPG guidelines prescribed by the Endocrine Society [31], 90.83% (95% CI: 83.93%–94.94%) of the SLE cases in our study were found to have hypovitaminosis D (34.87% insufficient, 55.96% deficient), as opposed to 77.98% (95% CI: 69.33%–84.73%) of the healthy controls (40.37% insufficient, 37.61% deficient) of similar ethnicity, age and sex distribution, and recruited from the same geographical areas. Hypovitaminosis D was also widely prevalent in SLE patients from other parts of the world like Thailand (43.5% insufficient, 29.6% deficient), Saudi Arabia (89.7% deficient, 9.1% insufficient), Brazil (47% insufficient, 50% deficient), Spain (75% insufficient, 15% deficient) and France (65% insufficient, 15.9% deficient) [11], [12], [13], [18], [34].

Adequate vitamin D status seems to have a protective effect against autoimmune diseases like SLE such that its deficiency may determine SLE disease etiology, activity and/or aggravation [15], [19], [20], [21], [35]. The high prevalence of hypovitaminosis D in patient populations of SLE living in different geographical regions of the world and belonging to varied ethnic and socio-cultural backgrounds strongly support the association between SLE and vitamin D. Hypovitaminosis D is associated with winter flare ups [15], and high disease activity in SLE patients (both adults and children) [17], [18], [19], [20], [36], while SLE patients receiving vitamin D supplementation had less frequency of symptoms (e.g. fatigue) and they also required lower doses of medications [14]. A recent systematic review of randomized clinical trials indicated that therapeutic vitamin D supplementation led to marked reductions in SLE disease activity [37]. In contrast, Hiraki et al. failed to detect any significant relationship between dietary vitamin D intake during adolescence and subsequent development of SLE in adulthood [38]. In that study, the dietary intake of vitamin D was assessed using self-reported questionnaires, but the serum 25-OH-D levels were not reported, due to which the vitamin D status of the study participants could not be known. This limitation was crucial because dietary vitamin D intake (contributes to ~20% of body vitamin D stores) does not represent the major source of vitamin D in the body.

Our study reinforces the inverse relationship between vitamin D and SLE disease activity. Traditionally, vitamin D status has been largely viewed as a predictor of SLE disease activity. Our findings suggest that this inverse association may be two-way in nature. Patients with the lowest vitamin D category were found to have the highest SLEDAI score values in our study. Conversely, patients with the lowest SLEDAI category were found to have the best serum 25-OH-D concentrations. There is accumulating evidence that the link between

vitamin D and SLE is bidirectional [22], so that vitamin D may be both a cause and a consequence of SLE onset/progression [39], [40]. The results of our analyses may be a reflection of this trend. On the one hand, we found that vitamin D deficiency was an independent variable influencing high disease activity, even after potential confounders were accounted for. The SLE patients with vitamin D deficiency were nearly 3.5 times more likely to have high or very high disease activity scores. Clinical and animal model studies support this observation between vitamin D status and SLE clinical course/disease activity, which appears to be linked to modulation of interferon levels [17], maintenance of adequate proportion of $CD4^+/CD8^+$ double positive peripheral T-lymphocytes [21], influence on leukocyte telomere length and cellular aging [16], vitamin D receptor (*VDR*) gene polymorphism [41], regulation of expression of autophagy related genes in peripheral blood mononuclear cells and T-cell subsets [42], controlling B-cell homeostasis and restoring the regulatory T-cell and effector T-cell balance [43] and upregulating the $FoxP3^+/IL\text{-}17A$ ratio in $CD4^+$ T-cells [44]. On the other hand, when factors influencing vitamin D deficiency were investigated in our sample, it was found that having raised disease activity (SLEDAI score > 10) was a major determining factor. Traditionally, the high prevalence of vitamin D deficiency in SLE is often attributed to avoiding sun-exposure due to photosensitivity [10], [11]. Additionally, factors such as renal involvement [10], [13], or influence of medications like HCQ [11], and corticosteroids [14] are suggested as responsible for low 25-OH-D levels in SLE. However, even after controlling for these confounders, patients with SLEDAI > 10 had approximately 4 times greater risk of being vitamin D deficient.

Endogenous vitamin D synthesis is dependent upon cutaneous UVB exposure, which in turn may be influenced by factors such as clothing worn, time spent outdoors for recreation, walking, etc. Unavailability of adequate information from the study participants about these variables was a limitation of our study. Further, although we documented the overall dietary practices (vegetarian vs. non-vegetarian) of the study participants, yet information about the specific food items, their frequency and potion size could not be reliably obtained.

Conclusion

In summary, hypovitaminosis D is widely present in SLE patients from northeast India. Nearly 91% of patients had vitamin D deficiency or insufficiency. Therefore, the evaluation of vitamin D status in SLE is important. The pilot data from this study support the inverse association between vitamin D status and disease activity in SLE. It further suggests that the relationship between vitamin D deficiency and SLE disease activity may be bidirectional. Vitamin D status may be associated both as an outcome and determinant of disease activity in SLE. Longitudinal studies in this line in the future would be useful in identifying the temporal connection between SLE and vitamin D, and thereby help in establishing the direction of causality.

Author Statement

Research funding: None.

Conflict of interest: Authors state no conflicts of interest.

Informed consent: Voluntary informed written consent was procured from all the participants of the study.

Ethical approval: The research related to human use complied with all the relevant national regulations and institutional policies and was performed in accordance to the tenets of the Helsinki Declaration and has been approved by the institutional ethical committee.

Authors' contributions: SK and CD carried out the conceptualization. KB and BB contributed to the design and carried out the literature review. CD was involved in enrolment of study participants, and the collection of their clinico-laboratory information, under the supervision of SK. CD contributed to data management. KB analyzed and interpreted the data with inputs from BB. KB wrote the manuscript with inputs from CD. SK and BB helped in critically revising the manuscript. All authors accept responsibility of the manuscript.

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