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Vitamin D Level in SLE Patients with or without Renal Involvement and its Relationship with Disease Activity (SLEDAI)

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Abstract

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem involvement, with lupus nephritis (LN) being a major complication. Vitamin D, known for its immunomodulatory properties, has been implicated in SLE pathogenesis, with deficiency potentially contributing to increased disease activity.

Aim of the study: This study aimed to evaluate serum vitamin D levels in SLE patients with and without renal involvement and investigate their correlation with disease activity, as measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

Methods: A cross-sectional study was conducted at Dhaka Medical College Hospital, Bangladesh, over one year (April 2018–March 2019). A total of 130 participants were enrolled, including SLE patients with nephropathy (n=50), SLE patients without nephropathy (n=50), and healthy controls (n=30). Serum vitamin D levels were measured and compared across groups, and correlations with disease activity were assessed using statistical analyses.

Result: Vitamin D levels were significantly lower in SLE patients with nephropathy (14.92 ± 3.76 ng/mL) compared to those without nephropathy (19.65 ± 6.15 ng/mL) and healthy controls (23.95 ± 8.81 ng/mL) ($p<0.001$). A negative correlation was observed between vitamin D levels and SLEDAI scores, indicating that lower vitamin D levels were associated with higher disease activity.

Conclusion: SLE patients, particularly those with renal involvement, exhibit significant vitamin D deficiency, which correlates with increased disease activity. These findings highlight the potential need for routine vitamin D screening and supplementation in SLE management to mitigate disease progression.

Keywords: Systemic lupus erythematosus; Lupus nephritis; Vitamin D deficiency; Disease activity; SLEDAI; Immunomodulation

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by multisystem involvement and a broad spectrum of clinical manifestations. It primarily affects young women and is influenced by genetic, environmental, and immunological factors [1]. Among the various systemic complications, lupus nephritis (LN) remains a significant cause of morbidity and mortality in SLE patients [2]. Vitamin D, a fat-soluble secosteroid, plays a crucial role in calcium homeostasis and bone metabolism. However,

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emerging evidence suggests that vitamin D also possesses immunomodulatory properties, influencing both innate and adaptive immunity [3]. Several studies indicate an association between vitamin D deficiency and increased disease activity in autoimmune conditions, including SLE [4]. Vitamin D deficiency is highly prevalent in SLE patients and is attributed to multiple factors, such as reduced sun exposure, use of photoprotective measures, chronic steroid therapy, and impaired renal function [5]. The active form of vitamin D, 1,25-dihydroxyvitamin D3, exerts its immunomodulatory effects by binding to the vitamin D receptor (VDR) expressed on various immune cells, including T lymphocytes, B cells, and dendritic cells. This interaction modulates cytokine production, inhibits autoantibody synthesis, and suppresses inflammatory responses, thereby playing a protective role in autoimmune diseases [6]. The impact of vitamin D levels on SLE disease activity, particularly in relation to renal involvement, remains a topic of considerable interest. Previous studies have reported inconsistent findings regarding the relationship between serum vitamin D concentrations and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores, which assess disease severity [7]. Some investigations have demonstrated an inverse correlation, suggesting that lower vitamin D levels are associated with increased disease activity and renal involvement [8]. In contrast, other studies have found no significant association [9]. The discrepancies in findings may be due to variations in study design, sample size, ethnicity, and the criteria used to define vitamin D deficiency. Lupus nephritis, a major complication of SLE, occurs in a substantial proportion of patients and significantly influences disease prognosis. The inflammatory and fibrotic processes in lupus nephritis may be exacerbated by vitamin D deficiency, as vitamin D has been shown to exert anti-inflammatory and antifibrotic effects in renal tissue [10]. Additionally, vitamin D insufficiency has been linked to increased proteinuria, renal dysfunction, and a higher risk of progression to end-stage renal disease (ESRD) [11]. Understanding the relationship between vitamin D status and lupus nephritis may provide insights into potential therapeutic interventions aimed at improving clinical outcomes in SLE patients. By elucidating the role of vitamin D in SLE pathophysiology, particularly in lupus nephritis, this research may contribute to the growing body of evidence supporting the need for vitamin D supplementation as an adjunctive therapeutic strategy in SLE management [12]. This study aims to evaluate vitamin D levels in SLE patients with and without renal involvement and to investigate its correlation with disease activity as measured by SLEDAI scores.

Methodology & Materials

This Cross-sectional study was conducted in the Department of Nephrology, Dhaka Medical College, Dhaka, Bangladesh. The study spanned 1 year, from April 2018 to March 2019, and aimed to investigate patients diagnosed with Systemic Lupus Erythematosus (SLE) with and without nephropathy. Using a purposive sampling method, the study included a total of 80 participants, divided into three groups as follows:

- **Group A (n=50):** Diagnosed case of SLE with nephropathy (case)
- **Group B (n=50):** Diagnosed case of SLE without nephropathy (comparator)
- **Group C (n=30):** Apparently healthy individuals (control)

Inclusion Criteria

Group A:

- o Age >18 years
- o Diagnosed with SLE
- o Features consistent with renal involvement, confirmed by investigations (Urine R/M/E, UTP)

Group B:

- o Age >18 years
- o Diagnosed with SLE
- o No clinical or biochemical evidence of renal involvement

Group C:

- o Age >18 years
- o Apparently healthy individuals

Exclusion Criteria

- Age <18 years
- Postmenopausal women
- Known or history of metabolic bone disorders, malabsorption, thyroid disease
- Immobilization, or use of drugs that affect bone homeostasis (e.g., phenytoin, methotrexate, cyclosporine, vitamin D, oral contraceptives)
- Diagnosed with other autoimmune diseases or had previously been on calcitriol or alendronate
- Pre-existing renal disease
- Co-morbidities affecting renal function

Ethical Considerations

Ethical clearance was obtained from the Ethical Review Committee (ERC) of Dhaka Medical College. The confidentiality of participants' information was strictly maintained, with access limited to authorized personnel only.

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Informed written consent was obtained from all participants, in which the study's nature, purpose, procedures, and the participants' rights were clearly outlined. These rights included the right to refuse, accept, or withdraw from the study at any point. Furthermore, participants did not receive any financial benefits from participating in the study.

Data Collection

Following their attendance at the Department of Nephrology, all patients were assessed and managed accordingly. Participants were selected based on the inclusion and exclusion criteria. After informing the participants about the study's aims, objectives, and procedures, written informed consent was obtained. A comprehensive history was taken, focusing on clinical features and disease duration, along with physical examinations. All patients underwent routine hematological (Complete Blood Count, Erythrocyte Sedimentation Rate), biochemical (serum creatinine, serum calcium), and immunological (Anti-Nuclear Antibodies, Anti-dsDNA) tests. Additionally, serum 25(OH) D levels and complete urine analysis were performed for all patients. Investigations conducted included Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Urine R/M/E, Urine Protein (UTP), Anti-Nuclear Antibodies (ANA), Anti-Ds DNA, Anti-Sm Antibody, Complement C3, C4, Serum Creatinine, Serum Vitamin D, Serum Calcium, Serum Parathyroid Hormone (PTH), Serum Albumin, and Ultrasonography (USG) of the whole abdomen. Study variables included Age, Sex, BMI, SLE Disease Activity Index (SLEDAI) score, CBC, Urine R/M/E, UTP, Anti-dsDNA, Serum Creatinine, and Vitamin D levels. In necessary cases, renal biopsy was performed with strict aseptic precautions. Diagnosis of SLE was based on the American College of Rheumatology Classification Criteria, requiring the presence of four or more of the 11 criteria either serially or simultaneously. Lupus nephritis was confirmed according to the "American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis" [13]. Disease activity in SLE patients was estimated using the SLEDAI score [14]. A semi-structured questionnaire and checklist were also used for data collection.

Statistical Analysis

Data was collected, tabulated, and analyzed using SPSS version 22. Descriptive statistics (mean and standard deviation) were used for quantitative data, while frequencies and percentages were used for qualitative data. Parametric tests (Student's t-test) were used for normally distributed data, and non-parametric tests (Mann–Whitney U test) were used for non-normally distributed data. The Chi-square test was applied to examine associations between qualitative variables. Pearson's correlation was used to determine associations between two quantitative variables. A repeated-measure ANOVA, with post-hoc analysis, was used to compare Vitamin D levels among the three groups. A p-value of ≤ 0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of the study population, consisting of 130 participants, were analyzed across three groups: Group A (n=50), Group B (n=50), and Group C (n=30). Age distribution did not differ significantly between groups, with the mean ages being 24.8±8.52 years for Group A, 25.48±8.42 years for Group B, and 28.00±8.41 years for Group C (p=0.251). Gender distribution was predominantly female in all groups, and BMI values were similar across groups (p=0.93) (Table 1). Clinical symptoms, signs, and laboratory findings were compared between SLE patients with and without nephropathy in Table 2. Group A showed significantly higher rates of generalized swelling (16%), leg swelling (30%), and facial puffiness (8%) compared to Group B, where these symptoms were absent (p=0.003, p<0.001, p=0.041, respectively). Hair fall was more common in Group B (18%) but the difference was not significant (p=0.065). Proteinuria (94% in Group A vs. 34% in Group B) and higher urinary total protein (UTP) levels were significantly more common in Group A (p<0.001). Group A also had higher WBC counts (7.80±4.08 × 10^6/L vs. 6.36±2.44 × 10^6/L, p=0.035) and lower platelet counts (264.68±159.04 × 10^6/L vs. 294.96±105.32 × 10^6/L, p=0.007), while serum creatinine levels were higher in Group A (1.88±2.80 mg/dL vs. 0.93±0.28 mg/dL, p=0.021). The SLE disease activity index (SLEDAI) scores showed that Group A had the majority in the moderate activity category (78%), whereas Group B had most patients in the mild activity category (62%) (p<0.001) (Table 3). Table 4 presents the disease duration of SLE patients. The median duration of SLE disease was 5.5 months in Group A and 4 months in Group B. The total median duration for all patients was 4 months. The range of disease duration was similar between the groups, with Group A spanning from 1 to 72 months, Group B from 1 to 36 months, and the total range for all patients from 1 to 72 months. No statistically significant difference was observed in the disease duration between the two groups (p=0.652). Vitamin D levels were significantly lower in Group A (14.92±3.76 ng/ml) compared to Group B (19.65±6.15 ng/ml) and Group C (23.95±8.81 ng/ml), with 92% of Group A being deficient (<20 ng/ml) (p<0.001) (Table 5).

Discussion

Vitamin D deficiency is increasingly linked to SLE, with growing evidence suggesting its role in disease activity and organ involvement. Renal involvement in SLE may further exacerbate vitamin D deficiency due to impaired renal synthesis and disease-related factors. In this study, the mean age of SLE patients with renal involvement was 24.8 ± 8.52

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Table 1: Demographics characteristics of the study population (N = 100).

Characteristics	Group A (n=50) n (%)	Group B (n=50) n (%)	Group C (n=30) n (%)	p-value
Age Group (years)				
≤15	7 (14)	2 (4)	1 (3.3)	0.123
16–20	11 (22)	16 (32)	5 (16.7)	
21–25	15 (30)	14 (28)	8 (26.7)	
26–30	10 (20)	4 (8)	6 (20)	
31–35	1 (2)	8 (16)	3 (10)	
36–40	2 (4)	4 (8)	4 (13.3)	
41–45	4 (8)	2 (4)	3 (10)	
Mean ± SD	24.8 ± 8.52	25.48 ± 8.42	28.00 ± 8.41	0.251
Gender				
Male	7 (14)	4 (8)	3 (10)	0.619
Female	43 (86)	46 (92)	27 (90)	
BMI (kg/m^2)				
Mean ± SD	21.43±1.90	21.56±1.93	21.57±1.95	0.93

Table 2: Clinical Symptoms and Signs in SLE Patients with and Without Nephropathy (N = 100).

Variable	Group A (n=50) n (%)	Group B (n=50) n (%)	p-value
Symptoms			
Generalized swelling	8 (16)	0	0.003
Leg swelling	15 (30)	0	<0.001
Facial puffiness	4 (8)	0	0.041
Hair fall	3 (6)	9 (18)	0.065
Oral ulcer	7 (14)	7 (14)	1
Altered consciousness	1 (2)	0	0.315
Generalized body ache	8 (16)	10 (20)	0.603
Erythematous rash	4 (8)	10 (20)	0.084
Joint pain	13 (26)	18 (36)	0.28
Signs			
Anemia	4 (8)	10 (20)	0.084
Oedema	22 (44)	0	<0.001
Hypertension	4 (8)	0	0.041
Investigations			
Proteinuria	47 (94)	17 (34)	<0.001
UTP, g/d (Mean ± SD)	2.15 ± 0.30	0.28 ± 0.03	<0.001
Anti-DSDNA Positive	41 (82)	39 (78)	0.617
Hematological Profile			
Hemoglobin (g/dL)	10.30 ± 1.82	10.40 ± 1.82	0.781
WBC (×10^6/L)	7.80 ± 4.08	6.36 ± 2.44	0.035
Platelet (×10^6/L)	264.68 ± 159.04	294.96 ± 105.32	0.007
ESR (mm in 1st hour)	43.72 ± 41.11	46.28 ± 39.67	0.679
Serum Creatinine (mg/dL)	1.88 ± 2.80	0.93 ± 0.28	0.021

Table 3: SLE disease activity index (SLEDAI) score of patients (N=100).

SLEDAI	Group A (n=50)	Group B (n=50)	Total (n=100)	Total (n=100)
Activity Category				
No activity (0)	0	19 (38)	19 (19)	
Mild activity (1 – 5)	3 (6)	31 (62)	34 (34)	
Moderate activity (6 – 10)	39 (78)	0	39 (39)	<0.001
Severe activity (11 – 19)	8 (16)	0	8 (8)	
Very severe activity (≥20)	0	0	0	

Table 4: Disease duration of SLE patients (N=100).

Duration (months)	Group A (n=50)	Group B (n=50)	Total (n=100)	p value
Median	5.5	4	4	0.652
Range	1 – 72	1 – 36	1 – 72	

Table 5: Vitamin D Status of Study Population (N=130).

Variable	Group A (n=50) n (%)	Group B (n=50) n (%)	Group C (n=30) n (%)	p-value
Vitamin D (ng/ml)	14.92 ± 3.76	19.65 ± 6.15	23.95 ± 8.81	0.001
Vitamin D Level Categories				
Deficient (<20 ng/ml)	46 (92)	26 (52)	12 (40)	<0.001
Insufficient (21–29 ng/ml)	4 (8)	22 (44)	14 (46.7)	
Sufficient (30–100 ng/ml)	0	2 (4)	4 (13.3)	

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years, while those without renal involvement had a mean age of 25.48 ± 8.42 years. Mandal et al. reported a similar mean age of 28.14 ± 8.43 years [15]. SLE affects all ethnicities, ages, and sexes, but 90% of new cases occur in women of childbearing age [16], possibly due to varying health-seeking behaviors across regions. Females were more prevalent in this study, with 86% of SLE patients with renal involvement and 92% without. Mandal et al. reported a similar distribution, with 97% females and 3% males [15]. This female predominance is likely influenced by endogenous sex hormones, though the rarity of SLE in men remains unclear [17]. In this study, joint pain was the most common presentation in group A (26%) and group B (36%), followed by generalized body ache (16%), rash (8%), and anemia (8%) in group A, while rash and anemia were observed in 20% of group B. Among renal involvement features, patients presented with generalized swelling (16%), leg swelling (30%), edema (44%), hypertension (8%), and proteinuria (86%). Similarly, Devadass et al. reported arthritis (43.5%), rash (39.1%), and fever (30.4%) as the most common initial symptoms in SLE patients with renal involvement [18]. In contrast, Mandal et al. reported common clinical manifestations in SLE patients, including arthritis (60%), oral ulcers (59%), malar rash (57%), photosensitivity rash (26%), discoid rash (11%), neuropsychiatric disease (9%), serositis (5%), myocarditis (2%), nephritis (37%), and vasculitis (13%) [15]. The clinical course of SLE is highly variable among patients and may be characterized by periods of remissions and of chronic or acute relapses [19]. In this study, vitamin D levels were measured in all patients and healthy controls, with mean levels of 14.92 ± 3.76 ng/ml in group A, 19.65 ± 6.15 ng/ml in group B, and 23.95 ± 8.81 ng/ml in group C. These findings align with Korah et al., who reported lower serum 25(OH)D levels in SLE patients with and without nephropathy compared to healthy controls, with mean levels of 36.6 ± 11.8 nmol/L, 46.2 ± 13.5 nmol/L, and 79.1 ± 9.3 nmol/L, respectively [8]. Additionally, Kamen et al. suggested a link between vitamin D deficiency and lupus nephritis [20]. Vitamin D deficiency in healthy controls was notably higher in this study compared to the findings of Korah et al. [8]. This may be attributed to the overall high prevalence of vitamin D deficiency among women in Bangladesh. In our study, vitamin D levels were categorized as deficient (<20 ng/ml), insufficient (21–29 ng/ml), and sufficient (≥30 ng/ml). It was found that the majority of SLE patients, both with renal involvement (92%) and without (52%), were vitamin D deficient, compared to 40% of controls. Among patients with lupus nephritis, 8% had insufficient vitamin D, while 44% of those without renal involvement were insufficient. These findings are consistent with Handono et al., who reported 55.56% of SLE patients with vitamin D deficiency, 24.7% with insufficiency, and 20.37% with normal levels [20]. Another study by Kalim et al. reported vitamin D deficiency, insufficiency, and normal levels in SLE patients at 25.5%, 61.8%, and 14.7%, respectively [21]. These findings further support that low vitamin D levels are common in SLE patients, indicating a higher risk of vitamin D insufficiency in this population [20]. The high prevalence of vitamin D levels below normal in SLE patients, ranging from 50-75%, is consistent with other studies, though these were conducted in different latitudes and ethnic groups [22,11]. This low concentration of vitamin D may be attributed to factors such as limited sun exposure, use of sun-blocking agents, lack of dietary intake, and wearing full-covered clothing [20,23]. Additionally, it is known that SLE patients produce anti-vitamin D antibodies [3]. Examining the effect of sun exposure duration, use of sun-blocking agents, serum anti-vitamin D antibodies, and dietary intake was beyond the scope of this study. Overall, the median SLEDAI score for patients with renal involvement was 8 (range 4–18), while for patients without renal involvement, it was 2 (range 0–4). The mean SLEDAI was significantly higher in patients with renal involvement ($p<0.05$). These findings are consistent with those of Korah et al., who reported a significantly higher SLEDAI score in patients with renal involvement [6]. Additionally, Pearson's correlation coefficient revealed a negative linear correlation between the SLEDAI score and vitamin D levels in both lupus nephritis and SLE without renal involvement patients ($r = -0.591$, $p < 0.001$ and $r = -0.472$, $p < 0.001$, respectively). This indicates that as vitamin D levels increased, the SLEDAI score significantly decreased, and vice versa. Similar correlations were found in studies by Handono et al. ($p < 0.0000$, $r = -0.659$) and Mandal et al. ($p < 0.0001$, $r = -0.42$) [15,20]. However, a study by Kim and colleagues in Korea found no correlation between vitamin D levels and disease activity in SLE patients [21]. Considering the immunoregulatory functions of vitamin D, patients with SLE and low 25(OH) D serum levels would be expected to experience more severe and frequently active diseases. However, the data in the literature remains controversial, likely due to differences in methodologies, study designs, patient characteristics, and varied cutoff points for SLEDAI and 25(OH) D. Furthermore, the specific cutoff point at which 25(OH) D levels begin to influence disease activity is still not well established [24]. These results suggest that the association between vitamin D levels and disease activity is stronger in patients with more severe diseases, such as those with lupus nephritis. It is well established that SLE is associated with hypovitaminosis D, and current evidence indicates that vitamin D levels are significantly lower in SLE patients with nephritis.

Conclusion and Recommendations

In this study, it is observed that SLE patients have significantly low serum 25(OH) D levels, particularly in those with renal involvement. This low vitamin D is also negatively correlated with SLE disease activity index score.

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Recommendations

- SLE patients with renal involvement should screen vitamin D.
- Supplementation of calcium and vitamin D should be administered particularly for those patients with renal involvement.
- Further studies of larger sample size are recommended.

Limitations of the study

- Sample size was not representative to generalize the findings.
- Cumulative effects of hydroxychloroquine and corticosteroid in vitamin D level could not be evaluated.

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Ethical approval: The study was approved by the Institutional Ethics Committee.

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