AJPMHS
GLOBAL RESEARCH NETWORK

AMERICAN Journal of Pediatric Medicine and Health Sciences
Volume 2, Issue 9, 2024 ISSN (E): 2993-2149

Features of the Course of Sle with Kidney Damage Depending on the Level of Vitamin D

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Abstract: The objective of this research was to examine the association between 25-hydroxycalciferol status and disease activity in patients diagnosed with Systemic Lupus Erythematosus (SLE) and concurrent renal impairment. Additionally, the study aimed to evaluate the correlation of 25-hydroxycalciferol levels with clinical and laboratory data, exploring the possibility of utilizing them as biomarkers for assessing renal activity in individuals with lupus nephritis. A total of 128 participants were enrolled in the study and subsequently categorized into three distinct groups: group I (SLE active lupus nephritis group) which included 53 patients with SLE, and group II (SLE/inactive LN), which included 57 patients and group III, which included 30 practically healthy people from the control group. Patients were subjected to a complete history and clinical examination. All participants underwent standardized assessments, including SLEDAI-2K evaluation for disease activity and serum 25-hydroxycalciferol level measurements. Results: The findings of this study revealed a significant decrease in serum 25-hydroxycalciferol levels among patients diagnosed with SLE/LN when compared to the healthy control group. Furthermore, patients experiencing active lupus nephritis demonstrated even lower levels of 25-hydroxycalciferol. This suggests a higher prevalence of 25-hydroxycalciferol insufficiency and deficiency within the SLE/LN patient population, particularly during periods of active disease. A statistically significant association was identified between reduced serum 25-hydroxycalciferol levels and the presence of fatigue, photosensitivity, and hypertension. Regression analysis highlighted lupus nephritis, photosensitivity, and high blood pressure as the most influential factors affecting serum 25-hydroxycalciferol levels in individuals with SLE.

Keywords: systemic lupus erythematosus, lupus nephritis, 25-hydroxycalciferol, serum 25-hydroxycalciferol levels, 25-hydroxy25-hydroxycalciferol.

Systemic lupus erythematosus (SLE), a chronic autoimmune disorder with a complex pathogenesis, presents a significant health concern due to its widespread prevalence across the globe [1], [2], [3]. Although SLE affects both men and women, its incidence is higher in women across all age and demographic groups. Notably, women of reproductive age (15–44 years), the ratio between men and women is the highest [4]. SLE can affect any organ or system of the body [5], [6], [7]. A common complication of SLE is lupus nephritis, a kidney disease that occurs in up to 50% of SLE patients [6, 8]. Unfortunately, the exact pathogenesis of SLE is still not fully

understood [9]. However, studies show that the presence and interaction of autoreactive cells in SLE patients leads to the production of autoantibodies against autoantigens [6], [10]. Subsequently, autoantibodies bind to autoantigens with subsequent formation of immune complexes (ICs) that activate inflammatory responses [1], [6], [11], [12]. In SLE, kidney damage remains one of the most severe conditions and the prognosis is unfavorable [30]. The extent of renal involvement, specifically the development and progression of lupus nephritis, plays a critical role in determining the long-term outcomes for patients diagnosed with SLE. Complications associated with lupus nephritis pose a substantial threat to survival and represent the primary cause of death among individuals with SLE [14].

Beyond its established role in calcium homeostasis and bone metabolism, 25-hydroxycalciferol exhibits significant immunomodulatory and anti-inflammatory properties [1]. Studies have demonstrated the expression of VDRs on the surface of multiple immune cell types, coupled with the capacity of these cells to synthesize 1α-hydroxylase, the enzyme responsible for converting 25-hydroxycalciferol into its active form within lymphatic tissue microenvironments. These findings strongly support the involvement of 25-hydroxycalciferol in immune system regulation [4,5]. Calcitriol also prevents excessive activation of the renin-angiotensin-aldosterone system [15], which helps reduce the severity of arterial hypertension.

Given that kidney damage negatively impacts the 1-hydroxylation process crucial for activating 25-hydroxycalciferol, it stands as a significant predictor of 25-hydroxycalciferol deficiency (levels <10 ng/ml) in SLE patients. Consequently, numerous studies have explored the potential relationship between low 25-hydroxycalciferol levels and various aspects of SLE [17, 21]. These include common symptoms such as musculoskeletal pain, fatigue, and depression, as well as disease activity [11, 12], with some studies demonstrating an inverse correlation and others reporting no significant association [13].

This study investigated the association between 25-hydroxycalciferol levels and disease activity in SLE patients, specifically comparing those with active and inactive lupus nephritis (LN), and further explored the relationship between 25-hydroxycalciferol levels and clinical and laboratory parameters within these groups.

Methods

The study cohort comprised 108 patients diagnosed with systemic lupus erythematosus (SLE), recruited from the rheumatology and nephrology departments between March 2022 and December 2023. The cohort was further divided into two groups: 55 patients with inactive lupus nephritis (SLE/inactive LN) and 53 patients with active lupus nephritis (SLE/active LN). All included patients satisfied a minimum of 4 out of the 11 American College of Rheumatology (ACR) criteria established in 1997 for SLE diagnosis [18]. Additionally, the study adhered to the ACR criteria for LN classification [19]: Clinical assessment of lupus nephritis (LN) activity was performed using the SLICC RA/RE. According to this scale, proteinuria 0.5-1 g/day corresponded to 3 points, proteinuria 1-3 g/day - 5 points, proteinuria >3 g/day - 11 points, erythrocyturia more than 10 - 3 points, leukocyturia more than 10 - 1 point. The index is calculated by summing the points [18,19].

What is more, 20 healthy control group people were included in the study. The study did not include patients with kidney diseases caused by other causes, patients on program dialysis, with malignant neoplasms, pregnant women, patients under 18 years of age, and patients receiving 25-hydroxycalciferol therapy.

All study participants received a medical history, medical record review, and physical examination. During examination, age, gender, and duration of the disease were recorded. All patients, apart from basic therapy, did not take 25-hydroxycalciferol before the start of our study. All participants in our study underwent the following laboratory and instrumental studies: general urinalysis, complete blood count, erythrocyte sedimentation rate (ESR), C-reactive

protein (CRP), serum creatinine, the presence of antinuclear autoantibodies (ANA) and anti-ds-DNA . To check for the presence of casts in the urine, 24-hour urine proteinuria was examined in patients. Clinical assessment of SLE activity was carried out using the SLEDAI2K index. VD status was determined by measuring serum concentrations of 25-hydroxyvitamin (25-hydroxycalciferol), which is the major circulating form of VD. VD deficiency was defined as a serum 25-hydroxy25-hydroxycalciferol level <30 ng/mL and greater than 15 ng/mL, whereas VD deficiency was defined as a serum 25-hydroxy25-hydroxycalciferol level <15 ng/mL. In addition, all patients underwent Doppler sonography of the kidneys and 24-hour blood pressure monitoring.

Statistical analyses were conducted utilizing SPSS for Windows, version 20.0. Continuous data were expressed as mean ± standard deviation (SD), and categorical data were expressed as number and percentage. Correlations between serum 25-hydroxy25-hydroxycalciferol levels and continuous data were assessed using the correlation coefficient test.

Results

The study included 55 patients with SLE/inactive LN, 53 patients with SLE/active LN and 20 healthy controls. The SLE/inactive LN group included 54 women (98.2%) and 1 man (1.8%); The study population exhibited an age range of 22 to 55 years, with a mean age of 37.2 years and a standard deviation of 9.1 years. The duration of systemic lupus erythematosus (SLE) among the participants varied from 2 to 18 years, with an average disease duration of 9.0 years and a standard deviation of 4.3 years. 50 (94.3%) women and 3 (5.7%) men, the group of patients consisted of patients with active lupus nephritis whose age ranged from 26 to 53 years with an average value of 39.7 ± 8.8 years and disease duration ranged from 1 to 15 years with a mean of 7.6 ± 3.7 years. 17 women (85.0%) and 3 men (15.0%) made up the control group, where their age ranged from 25 to 53 years with an average of 41.3 ± 7.5 years. All groups were comparable to each other, as there were no differences in age and gender composition between the groups.

Comparison of serum 25-hydroxycalciferol levels between groups

When comparing 25-hydroxycalciferol levels between groups, in the group of patients with active lupus nephritis, the results of the analysis were lower with a significant difference ($p = 0.015$) than in the group with inactive lupus nephritis (12.3 ± 0.8 ng/ml, and 19.8 ± 2. 4 ng/ml respectively). This figure was an even more significant difference between the control group (12.3 ± 0.8 vs. 34.6 ± 1.4 ng/ml, $p < 0.001$). In addition, the mean serum 25-hydroxy25-hydroxycalciferol level was lower in the SLE/inactive LN group than in the control group too (18.9 ± 2.4 vs. 34.6 ± 1.4 ng/mL, $p = 0.031$) **(Fig. 1).**

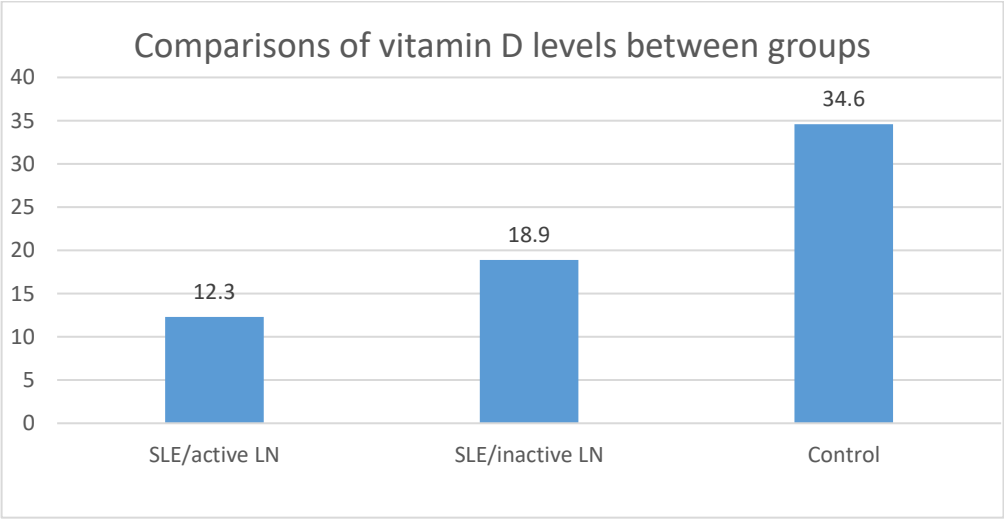

Figure 1. Comparison of serum 25-hydroxycalciferol levels (ng/ml) among patients with SLE/active LN, SLE/inactive LN, and controls.

Analysis of 25-hydroxycalciferol status revealed a notable disparity between the study groups. The highest incidence of 25-hydroxycalciferol deficiency was observed within the SLE group experiencing active lupus nephritis (LN), with 43.4% of individuals classified as deficient. The SLE group with inactive LN demonstrated a lower, yet still considerable, prevalence of deficiency at 29.2%, while in the control group it haven't met. Similarly, the incidence of VD failure is highest in the SLE/active LN group, then in the SLE/inactive LN group, and lowest in the control group at 54.5%, 50.9%, and 30%, respectively. These differences were significant P=0.05 (Table 1).

Table 1. Comparison of serum 25-hydroxycalciferol status between groups.

25-hydroxycalciferol					
25-hydroxycalciferol normal (≥30ng/ml)	14 (70%)	3 (5.6%)	9 (16.3%)	33,65	19,84
25-hydroxycalciferol failure (>15ng/ml)	6 (30%)	27 (50.9%)	30 (54.5%)	19,25	12,24
25-hydroxycalciferol deficit (<15 ng/ml)	-	23 (43.4%)	16 (29.2%)	-	-

Comparison of SLE/active LN and SLE/inactive LN groups

Table 2 provides a comprehensive comparison of clinical and laboratory findings between the SLE group with active lupus nephritis (LN) and the SLE group with inactive LN. The analysis revealed no statistically significant differences in the frequency of clinical manifestations or medication usage between the two groups. Additionally, no significant disparities were observed with respect to gender distribution, age, or disease duration. However, a notable distinction emerged regarding the course of the disease. The SLE/inactive LN group exhibited a higher proportion of patients diagnosed with chronic systemic lupus erythematosus, indicating a potentially more protracted disease course compared to the SLE/active LN group.

Table 2

Indicators	**SLE/ active LN (n=53)**	**SLE/ inactive LN (n=55)**	**Хи^2 P=0.05**
Fatigue	48 (90.5%)	43 (78.2%)	4,58
Mucosal ulcer	16 (30,2%)	12 (21,8%)	ND 0,98
Rash	44 (83.0%)	26 (47.3%)	15,12
Photosensitivity	49 (92.4%)	32 (58.2%)	16,91
Alopecia	38 (71.7%)	39 (70%)	ND 0,01
Arthritis	41 (77.3%)	36 (65.4%)	ND 1,87
Pleurisy	13 (24.6%)	16 (29.2%)	ND 0,23
Pericarditis	9	8	ND 0,12

	(16.9%)	(14.5%)	
Proteinuria	50 (94%)	44 (80%)	4,92
Hematuria	48 (90,5%)	38 (69%)	7,67
Leukocyturia	32 (60,4%)	30 (54,5%)	ND 0,38
Anti-dsDNA	35 (66 %)	16 (20%)	14,78
BP mmHg (systolic ≥ 140)	36 (67.9%)	21 (38.2%)	9,58
Blood pressure mmHg (diastolic ≥ 90)	38 (71.7%)	21 (38.2%)	12,23

In the SLE/active LN group, patients more often complained of fatigue (90.5%), arthralgia (77.3%), the appearance of ulcers on the mucous membranes (30.2%) and photodermatitis (92.4%), while in the SLE/inactive LN group these complaints were much less pronounced and widespread (photodermatitis in 78.2% of patients, arthralgia in 65.4% of patients, mucosal ulcers in 21.8% and photodermatitis in 58.2% of patients). At the same time, the most reliable Xi^2 indicators were: photosensitivity (16.91), rash (15.12), Anti-dsDNA (14.78), as well as diastolic blood pressure (12.23). Laboratory urine tests such as proteinuria were almost 15% more common in the SLE/active LN group than in the second group, patients with hematuria in the SLE/active LN group accounted for 90.5%, while in the SLE/inactive LN group it was found in 69% of patients. In addition, urinary parameters such as leukocyturia and cylindruria also occurred in a higher percentage in the SLE/active LN group than in the SLE/inactive LN group - 60.4% and 54.5%, respectively. Among patients with active lupus nephritis, 35 (66.03%) had a positive Anti-dsDNA result, and in the other group this figure was positive in 14 fewer patients (38.2% of patients). 71.7% of patients with active lupus nephritis had high blood pressure, in which an increase in diastolic pressure prevailed. Patients with hypertension among the inactive lupus nephritis group accounted for 38.2%. In the SLE/inactive LN group, high blood pressure was significantly less common than in the first group in 21 (38.2%) patients. Among the occurrence of clinical signs in the form of Alopecia, Pericarditis and Pleurisy in both groups, no significant differences were found and in the SLE/active LN group they were 71.7%, 16.9% and 24.6%, respectively, and in the SLE inactive LN group these indicators were 70%, 14.5% and 27.2% respectively.

Association between Serum 25-hydroxycalciferol Levels and Clinical/Laboratory Parameters in SLE Patients with Active and Inactive LN (Table 3).

Table 3 presents comparative clinical and laboratory data of patients with different levels of 25-hydroxycalciferol in the blood. In three categories of 25-hydroxycalciferol levels: normal, reduced and insufficient, clinical and laboratory data differed from each other. Many clinical and laboratory parameters were inversely correlated with a decrease in 25-hydroxycalciferol in the blood.

Table 3. Comparisons of 25-hydroxycalciferol with clinical and laboratory data.

Index	25-hydroxycalciferol normal n=12	25-hydroxycalciferol failure n=57	25-hydroxycalciferol deficit n=39
Fatigue	8 (66,7%)	50 (87.7%)	35 (89.7%)
Mucosal ulcer	-	11 (19.3%)	17 (43.5%)
Rash	6 (50%)	35 (61,4%)	29 (74,3 %)
Photosensitivity	8 (66.1%)	43 (75.4%)	30 (76.9%)
Alopecia	6 (50%)	35 (61.4%)	28 (71.7%)

Arthritis	4 (33.3%)	34 (59,6%)	29 (74.3%)
Pleurisy	2 (16.7%)	21 (36.8%)	10 (25.6%)
Pericarditis	1 (8.3%)	9 (15.8%)	5 (12.8%)
Proteinuria	8 (66,6%)	53 (92,9%)	37 (94.8%)
Hematuria	7 (58.2%)	49 (85.9%)	30 (76.9%)
Leukocyturia	5 (41.6%)	30 (52.6%)	27 (69.2%)
Anti-dsDNA	5 (41.6%)	32 (56.4%)	29 (74.3%)
BP mmHg (systolic ≥ 140)	1 (8.3%)	24 (42.1%)	32(82.1 %)
Blood pressure mmHg (diastolic ≥ 90)	1 (8.3%)	24 (42.1%)	34 (87.2 %)

Analysis of clinical signs revealed a notable association between 25-hydroxycalciferol deficiency and several key symptoms. Patients with lower 25-hydroxycalciferol levels exhibited a 10-20% higher prevalence of fatigue, malar rash (characteristic butterfly rash on the cheekbones), and photosensitivity compared to those with sufficient 25-hydroxycalciferol levels. Additionally, alopecia and joint damage were significantly more common in the 25-hydroxycalciferol deficient group, suggesting a potential link between 25-hydroxycalciferol status and these clinical manifestations. The incidence of arthritis was 33.3% among patients with normal 25-hydroxycalciferol levels, while among patients with 25-hydroxycalciferol deficiency and insufficiency this figure was higher (59.6% and 74.3%, respectively). Clinical criteria such as pleurisy and pericarditis did not reveal reliable correlation data with 25-hydroxycalciferol. Urinary laboratory parameters, such as proteinuria, were significantly inversely correlated with the level of 25-hydroxycalciferol in the blood. There was no relationship between 25-hydroxycalciferol and indicators such as leukocyturia and hematuria. Regarding anti-dsDNA antibodies, a marker often associated with SLE, a positive result was found in 41.6% of patients with normal 25-hydroxycalciferol levels. Similar proportions of positive anti-dsDNA results were observed in the groups with low 25-hydroxycalciferol levels and 25-hydroxycalciferol deficiency, suggesting no clear association between 25-hydroxycalciferol status and this particular autoimmune marker. This figure was significantly higher in 32 (56.4%) and 29 (74.3%) patients, respectively. The average level of systolic and diastolic blood pressure was also much higher than normal in patients with low 25-hydroxycalciferol in the blood.

Discussions:

According to the results of our study, reduced 25-hydroxycalciferol levels are more common among patients with SLE/LN than in the control group, and the course of lupus nephritis is more active in patients with 25-hydroxycalciferol deficiency. Further analysis revealed an inverse correlation between serum VD levels and SLE Disease Activity Index (SLE-DAI) scores, suggesting that lower 25-hydroxycalciferol levels may be associated with increased disease activity in SLE/LN patients. Moreover, low serum VD levels were significantly linked to specific clinical manifestations such as fatigue, photosensitivity, and elevated blood pressure. In patients with lower 25-hydroxycalciferol levels, proteinuria was more pronounced, and a higher proportion exhibited anti-dsDNA positivity. This study identified a notably high prevalence of 25-hydroxycalciferol insufficiency (52.7%) and deficiency (36.11%) among the participating SLE/LN patients. These findings align with previous research, including a study by Abaza et al. in Egypt, which reported a 73% prevalence of 25-hydroxycalciferol deficiency and 23% insufficiency among SLE patients, highlighting the widespread nature of 25-hydroxycalciferol deficiency in this patient population [21]. A similar study in the UK found that the overall prevalence of insufficiency and insufficient VD among patients with SLE was 69% and 39%, respectively [20,22]. In addition, a study by Korach et al found lower serum VD levels in patients with SLE compared to controls [23]. From these results, it can be said that low serum 25-hydroxycalciferol is prevalent among SLE patients. Moreover, our results also confirmed the

findings of studies conducted in other countries in different geographical locations. Also in studies from other countries, the incidence of low 25-hydroxycalciferol levels was as follows: in Brazilians 55%, [25] in Canadians 66.7%, [26] in Hungarians 81.9% and 98.8% in SLE patients in Saudi Arabia. Comparable to findings from Saudi Arabia, where cultural practices such as traditional clothing may restrict sunlight exposure and subsequently influence 25-hydroxycalciferol synthesis, the control group in this study also displayed a notable prevalence (exceeding 55%) of low 25-hydroxycalciferol levels. This observation is consistent with previous research that has consistently demonstrated significantly lower mean serum 25-hydroxycalciferol levels in SLE patient populations compared to healthy control groups. Interestingly, studies focusing on individuals with newly diagnosed SLE have reported a high prevalence of 25-hydroxycalciferol insufficiency (67.4%) and deficiency (17.9%), suggesting that insufficient 25-hydroxycalciferol levels may potentially be a risk factor for the development of SLE rather than a consequence of the disease.

Supporting this hypothesis, the results of the current study revealed that the SLE/active LN group exhibited the highest incidence of both 25-hydroxycalciferol deficiency and insufficiency, followed by the SLE/inactive LN group. The control group demonstrated the lowest prevalence of 25-hydroxycalciferol deficiency and insufficiency. In line with these observations, serum 25-hydroxycalciferol levels were significantly lower in the SLE/active LN group compared to both the SLE/inactive LN group and the healthy control group. In addition, patients in the SLE/inactive LN group had significantly lower mean serum 25-hydroxycalciferol levels than healthy controls. The findings of this study corroborate previous research by demonstrating a strong correlation between 25-hydroxycalciferol deficiency and lupus nephritis (LN) [23], with a particularly higher prevalence observed in patients with active SLE/LN [17]. This observation aligns with the results of other studies, which have suggested a higher prevalence, albeit not statistically significant [2] of 25-hydroxycalciferol deficits in patients with active LN compared to those with inactive LN.

Furthermore, the study revealed an inverse correlation between serum VD levels and SLE Disease Activity Index (SLE-DAI) scores in both the active and inactive LN groups [35], indicating a potential association between lower 25-hydroxycalciferol levels and increased disease activity [36]. This association is further supported by the finding that mean serum VD levels were significantly lower in patients with active SLE compared to those with inactive disease. The observed inverse correlation between VD and erythrocyte sedimentation rate (ESR) in both active and inactive LN groups further strengthens the hypothesis that 25-hydroxycalciferol may play a role in modulating inflammatory processes associated with SLE/LN. Notably, and consistent with observations from numerous other studies, no significant association was found between serum VD levels and the duration of SLE disease[25,29]. This suggests that the clinical manifestations and activity of the disease may exert a greater influence on 25-hydroxycalciferol status than the duration of illness.

The results of this study provide further evidence for the association between low serum VD levels and specific clinical manifestations in SLE/LN patients, particularly fatigue and photosensitivity. Moreover, an inverse relationship was observed between VD levels and both proteinuria and anti-dsDNA antibodies, which aligns with findings from previous studies [36]. Regression analysis confirmed the association of lower serum VD levels with both proteinuria and photosensitivity. Furthermore, analysis to identify predictors of low VD status revealed that LN activity (OR=13.3; $p<0.001$) and photosensitivity (OR=12.9; $p<0.001$) were the strongest factors associated with lower 25-hydroxycalciferol levels. Additionally, a higher incidence of arterial hypertension was observed in patients with low 25-hydroxycalciferol levels, suggesting a potential link between 25-hydroxycalciferol status and cardiovascular complications in SLE/LN. To further validate the findings of this study and explore their clinical implications, future research involving larger patient cohorts is recommended. Additionally, investigating the

potential impact of 25-hydroxycalciferol level correction on the prognosis and disease activity of SLE/LN represents a promising avenue for future research endeavors.

CONCLUSION

This study confirms that 25-hydroxycalciferol insufficiency and deficiency are highly prevalent among patients with SLE/LN, with a particularly increased prevalence observed in individuals with active disease. Lower serum 25-hydroxycalciferol levels demonstrated a significant correlation with higher disease activity as measured by the SLE Disease Activity Index (SLE-DAI) and elevated erythrocyte sedimentation rate (ESR). Furthermore, low serum VD levels were significantly associated with the presence of fatigue, photosensitivity, and hypertension, suggesting a potential role of 25-hydroxycalciferol in these clinical manifestations. The study identified the presence of lupus nephritis (LN), photosensitivity, and high blood pressure as key factors influencing serum 25-hydroxycalciferol levels in SLE patients.

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