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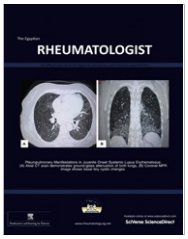

ORIGINAL ARTICLE

25-Hydroxy vitamin D levels and its relation to disease activity and cardiovascular risk factors in women with systemic lupus erythematosus

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KEYWORDS

25(OH) vitamin D;
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Abstract *Aim of the work:* To evaluate the associations of serum 25 hydroxy (OH) vitamin D [25(OH)D] levels with cardiovascular risk factors as well as disease activity in women with SLE.

Patients and methods: Fifty women with SLE as well as 30 controls were included in our study. Data collected included, demographics, SLE activity and damage assessments, cardiovascular risk factors, medications and laboratory assessment of inflammatory markers and 25(OH)D levels. Stepwise logistic regression analysis were used to estimate the association of 25(OH)D levels with cardiovascular risk factors.

Results: A significant lower 25(OH)D levels was found in SLE patients compared to controls ($P < 0.001$). A positive correlation was found between 25(OH)D and diastolic blood pressure, fasting blood sugar, cholesterol, triglycerides, LDL, BMI, as well as proteinuria and C3 levels. Furthermore, a significant positive correlation was found between 25(OH)D and the RT carotid artery

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stenosis and RT carotid artery plaque and the intima media thickness of both left and right carotid arteries. Lower 25(OH)D levels were also significantly associated with higher SLE disease activity and damage scores and steroid cumulative dose. Stepwise logistic regression analysis showed that higher BMI, diastolic blood pressure, cholesterol, triglycerides, LDL and diabetes mellitus act as predictors of lower 25(OH)D levels.

Conclusion: Our study found an association between lower 25(OH)D levels and increased cardiovascular disease (CVD) risk factors, as well as increased SLE disease activity and damage indices. Future studies are needed to determine relation of 25(OH)D and cardiovascular risk factors in patients with lupus.

1. Introduction

Several studies have suggested that 25-hydroxy vitamin 25(OH)D deficiency is an unrecognized contributor to the development of cardiovascular disease (CVD), cancer, and mortality. 1,25-Dihydroxy vitamin D affects the renin-angiotensin system [1], is associated with cardiac myocyte hypertrophy and has anti-inflammatory effects all of which may influence CVD risk [2]. Data from the third National Health and Nutrition Examination Survey (NHANES III) [3] found that adults with 25(OH)D levels <20 ng/ml compared with those with 25(OH)D levels $\geqslant 30$ ng/ml had an increased frequency of CVD, including coronary heart disease, heart failure, stroke, and peripheral arterial disease.

A leading cause of morbidity and mortality in women with SLE, including those who are premenopausal, is CVD [4] patients with lupus have an increased incidence of myocardial infarction up to 5 times that of the general population, with an age specific incidence in young women up to 50 times higher [5]. Evidence has been shown that like diabetes mellitus (DM), SLE itself is an independent risk factor for the development of atherosclerosis [6].

The identification of vitamin D receptor (VDR) in the cells involved in immune response and the discovery that activated dendritic cells produce vitamin D hormone suggested that vitamin D could exert immunoregulatory effects [7]. Vitamin D receptor is a member of the nuclear hormone receptor superfamily and has been identified in mononuclear cells, dendritic cells, antigen-presenting cells as well as activated T-B lymphocytes [8]. The effects of 1,25(OH)2D3 on the acquired, antigen-specific immune response is inhibition of both TH1and TH2 cell cytokine production, including IL-4, IL-6 [9,10], in addition vitamin D has been studied as a modifiable environmental factor [11] in autoimmune disease animal models, including SLE [12], experimental autoimmune encephalomyelitis [13], rheumatoid arthritis [14], type I DM [15] and inflammatory bowel disease [16]. SLE is the proto typical autoimmune disease and patients with SLE are known to have lower levels of 25(OH)D with measurements $\leqslant 20$ ng/ml [4] and in some cases, critically low at <10 ng/ml [17]. Lower levels of vitamin D have been shown to correlate with increased SLE disease activity [18] and studies using animal models of SLE demonstrated the attenuation of some manifestations with increasing vitamin D intake [3,12]. Our goal was to detect the association between 25-hydroxy vitamin D and cardiovascular risk factors in systemic lupus erythematosus patients and whether vitamin D levels are correlated with disease activity parameters.

2. Patients and methods

2.1. Study population

The study included 50 Egyptian SLE female patients with a mean age of 29.38 ± 9.2 years, fulfilling the 1982 revised criteria of the American Rheumatism Association for the classification of SLE [19], in addition to 30 healthy controls matched for age and sex with a mean age of 30.4 ± 7.1 years. All 50 patients and controls were premenopausal and were subjected to same sunlight exposure and clothing conditions. Three of the 50 SLE patients had history of cardiovascular accidents in the form of stroke which occurred in two patients and one patient developed myocardial infarction. All subjects were informed about the aim of the study and gave their consent. Patients were collected from the Rheumatology and Rehabilitation Department, Cairo and Fayoum University Hospitals.

2.2. Laboratory testing

Blood was drawn at the time of the study for analyses which included the following: antiphospholipid antibodies (aPL) (positive if IgG or IgM ACL was >40 IU/ml or if the lupus anticoagulants (“LAC”) was present. Antinuclear antibody testing (ANA), antiDNA using indirect immunofluorescence, C-reactive protein (CRP), serum complement (C3 and C4) levels by nephelometry and glomerular filtration rate were done to all patients. A complete blood picture, lipid profile, serum creatinine, liver function tests and electrolyte levels were tested for all enrolled cases.

25(OH)D levels was measured in the Department of Chemical Pathology, Cairo University Hospital by the 25(OH)D ^{125}I radioimmunoassay kit (Diasorin). The intra-assay coefficient of variation was 9.4%. Samples were measured in duplicate and the average value was reported. We defined vitamin D deficiency as <25 nmol/l while vitamin D insufficiency was between 25 and 75 nmol/l.

2.3. Traditional CVD risk factors

Information was obtained on age, smoking, diabetes, current estrogen use, current aspirin use, menopause status and history of cardiovascular disease (myocardial infarction, stroke, angina, transient ischemic attacks TIAs).

Systolic and diastolic blood pressure were determined using an average of 2 consecutive sittings 5 min apart. Blood

pressure recorded with patients seated. Hypertension was defined as an average systolic blood pressure $\geqslant$140 mmHg, an average diastolic blood pressure $\geqslant$90 mmHg, or the use of antihypertensive agents, in addition body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2) [20].

2.4. SLE related factors

Validated measures of lupus disease activity (SLEDAI) [21] and disease damage SLE international collaborating clinics (SLICC) were completed. Renal disease was considered if there is >0.5 g/day or 3^+ proteinuria and or the presence of cellular casts or had a renal biopsy sample with evidence of world health organization class IIb, III, IV, or V lupus nephritis [22]. History of steroid treatment was taken (current use and duration of treatment) as well as current use of hydroxychloroquine and immunosuppressant (including cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil and cyclosporine).

2.5. Ultrasonographic studies

All ultrasonographic studies were performed on the day of the study by an experienced radiologist and cardiologist.

Subclinical CVD was measured in the carotid arteries using carotid artery B-mode US. Carotid plaque was defined as a distinct area protruding into the vessel lumen that was at least 50% thicker than the surrounding areas. The outcome measure used for analyses was the presence or absence of plaque (plaque $\geqslant$ 1 versus plaque = 0).

The color Doppler map in the longitudinal and axial planes was used to identify the sites of luminal stenosis, atheromatous plaques or focal haemodynamically significant stenotic areas. Intima media thickness (IMT) was measured using specialized reading soft wear across 1 cm segments of both the RT and LT sides of the near and far walls of the distal common carotid artery and the far wall of the bulb and internal carotid artery. The mean of the average IMT reading across both sites was used for analysis.

Statistics: Statistical analysis, Statistical Package for Social Science program, version 15, was used for analysis of data. Data was presented as number (percent) and mean ± SD. Mann–Whitney test was used for the analysis of two quantitative data. Spearman correlation was used for detection of the relation between two variables. *P* value was considered significant if <0.05. Stepwise logistic regression analysis was performed; to estimate the association between 25(OH)D levels with cardiovascular risk factors. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of the included patients

Fifty patients with SLE were examined during this study, with a mean age of 29.3 ± 9.2 years and mean disease duration of 5.43 ± 4.56 years as well as 30 controls matched for age and sex. Out of the 50 SLE patients 18 patients had nephritis (36%) at some time during their disease course, and 12 patients reported they were current smokers (24%).

Self reported cardiovascular risk factors included 15 patients with hypertension (30%), 4 patients with diabetes mellitus (8%), 19 patients with hypercholesterolemia (38%) and 3 patients with history of cardiovascular disease (6%). In addition 9 subjects were found positive for anticardiolipin antibodies (ACL) IgG IgM (18%) and 7 study subjects were found to have positive lupus anticoagulants (14%). All patients were taking steroids (dose ranged from 15 to 50 mg/day), 45 patients on hydroxychloroquine (dose ranged from 200 to 400 mg/day), 25 patients on azathioprine (dose ranged from 100 to 150 mg/day) and 15 patients were receiving monthly cyclophosphamide pulse therapy depending on extent of renal lesion (dose ranged from 700 to 1000 mg). Radiological readings of the SLE patients found 5 patients with RT carotid artery stenosis, 4 patients with LT carotid artery stenosis, 4 patients with RT carotid plaque and 2 patients with LT carotid plaque. Patient descriptive data is shown in Table 1.

3.2. Prevalence of vitamin D deficiency

The mean level of 25(OH)D was 26.3 ± 5.58 nmol/l in the SLE group while it was 30.7 ± 4.68 nmol/l in the control group. Out of the 50 SLE patients recorded in our study, there were 18 patients (36%) who were vitamin D deficient (<25 nmol/l) and 32 patients (64%) who were vitamin D insufficient (25–75 nmol/l). Our control group included 17 vitamin D insufficient individuals (57%), 5 vitamin D deficient individuals (16.7%) and 8 with normal vitamin D levels. There was a positive significant difference between 25(OH)D levels in SLE patients and controls ($P < 0.001$) data is shown in Table 2 and graphically presented in Fig. 1.

3.3. 25-Hydroxy vitamin D levels and cardiovascular risk factors

No relationship was found between 25(OH)D and both lupus anticoagulants and anticardiolipin antibodies IgG, IgM ($P = 0.087$ and 0.197, respectively). In addition no correlation was found between 25(OH)D and cerebrovascular events or smoking ($P = 0.125$ and 0.127, respectively).

On the other hand a significant positive correlation was found between 25(OH)D diastolic blood pressure and fasting blood sugar ($P = 0.011$ and <0.001, respectively). While there was a significant negative correlation between BMI and 25(OH)D ($P < 0.001$). As regarding the correlation between the lipid profile in the SLE patients and 25(OH)D levels, a positive significant correlation was found with cholesterol, triglycerides and LDL levels ($P < 0.001$, <0.001 and 0.005, respectively).

Furthermore, a significant positive correlation was found between 25(OH)D and the RT carotid artery stenosis and RT carotid artery plaque ($P = 0.004$ and 0.013, respectively), in addition a positive correlation was found between 25(OH)D and the intima media thickness of both left and right carotid arteries ($P = 0.002$ and 0.010, respectively) (Table 3).

3.4. 25-Hydroxy vitamin D levels and SLE related factors

Our study showed a significant positive correlation between 25(OH)D and SLE SLEDAI and SLICC scores ($P = 0.006$ and 0.05, respectively).

Table 1 descriptive data of the studied SLE patients.

Characteristics	Value *n* (%), mean ± SD
Duration (years)	5.43 ± 4.56
Age mean	29.38 ± 9.2
Nephritis	26/50 (52%)
Serositis	10/50 (20%)
BMI (kg/m^2)	25.8 ± 6.4
SLEDAI score	17.5 ± 8.3
SLICC	0.56 ± 0.9
Cardiovascular risk factor	
Smokers	12/50 (24%)
Hypertension	15/50 (30%)
SBP (mmHg)	132.2 ± 14.99
DBP (mmHg)	87.4 ± 9.5
Hypercholesterolemia	19/50 (38%)
CVS	3/50 (6%)
RT CA stenosis	5/50 (10%)
LT CA stenosis	4/50 (8%)
RT CA plaque	4/50 (8%)
LT CA plaque	2/50 (4%)
Diabetes mellitus	7/50 (14%)
Laboratory data	
25(OH)D (nmol/l)	31.7 ± 12.5
FBS (mg/dl)	92.9 ± 16.5
Cholesterol (mg/dl)	194.4 ± 63.6
Triglycerides (mg/dl)	188.2 ± 65.6
HDL (mg/dl)	61.2 ± 15.0
LDL (mg/dl)	137.6 ± 37.1
ACL positive	9/50 (18%)
LAC positive	7/50 (14%)
CRP (mg/dl)	4.2 ± 10.2
Creatinine (mg/dl)	1.0 ± 1.4
Glomerular filtration rate (ml/min)	68.2 ± 19.2
C3 (mg/dl)	95 ± 32
C4 (mg/dl)	19.4 ± 8.9
Current medications	
Steroid dose (mg/day)	25.0 ± 8.03
Steroid duration/year	3.86 ± 2.57
HQN dose (mg/day)	380.0 ± 60.6
HQN duration/year	3.67 ± 2.4
Imuran dose (mg/day)	111.0 ± 40.7
Imuran duration (years)	2.47 ± 1.8
CYC cumulative dose (g)	3.79 ± 3.8

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CVS: coronoray vascular disease; CA: carotid artery; HDL: high density lipoprotein; LDL: low density lipoprotein; ACL: anticardiolpin antibodies; LAC: lupus anticoagulants.

Also a positive significant correlation was found between 25(OH)D levels, proteinuria and C3 levels ($P = 0.006$ and $< 0.00{,}1$ respectively). As regards medications given, there was a significant negative correlation between the duration of steroid use and its cumulative dose and 25(OH)D levels ($P = 0.008$ and 0.02, respectively), while there was no correlation between hydroxychloroquine or immunosuppressant and the levels of 25(OH)D.

3.5. Predictors of 25(OH)D levels

The following variables were independent predictors of lower 25(OH)D levels using stepwise logistic regression analysis, higher BMI (OR 0.83; 95% CI 0.78, 0.88), diastolic blood pressure (OR 0.70; 95% CI 0.58, 0.84), cholesterol (OR 0.70; 95% CI 0.63, 0.78), triglycerides (OR 0.66; 95% CI 0.55, 0.79), LDL (OR 0.62; 95% CI 0.46, 0.74) and DM (OR 0.59; 95% CI 0.47, 0.76) (Table 4).

4. Discussion

In SLE, many causes of vitamin D deficiency exist [23] with some of the most common causes being reduced skin synthesis and absorption of vitamin D due to sunscreen use, darker skin pigment, aging, season, latitude, and time of day [23,24]. These causes are particularly relevant in patients with lupus because of disease related photosensitivity and increased use of sunscreen.

Other lupus related factors that may contribute to vitamin D deficiency include renal disease [25], use of steroids that are thought to alter the metabolism of vitamin D [26] and hydroxylchloroquine [27].

Our findings in this study noting an association between CVD risk factors and low vitamin D levels are consistent with those reported in the general population [19].

Data from the third National Health and Nutrition Examination Survey (NHANES III) [19], showed that patients within the lowest vitamin D level (< 20 ng/ml), had a significantly increased prevalence of selected CVD risk factors (including a history of diabetes and elevated blood pressure, fasting blood glucose, BMI and triglycerides) when compared with the highest level (> 37 ng/ml).

In addition several studies have shown relationship between 25(OH)D level, CVD events, and CVD mortality, even after adjusting for traditional CVD risk factors [28]. Within the SLE population, no studies have documented an association between vitamin D levels and CVD risk factors or outcomes except that of Wu et al. [29] who found that lower 25(OH)D levels to be associated with several cardiovascular risk factors in the univariate model.

On the opposite of our study, Hsia et al. [30] found that calcium and vitamin D supplementation in healthy postmenopausal women aging 50–70 years, neither increased nor decreased the risk of myocardial infarction, coronary heart disease or death over a period of 7 years.

Table 2 25(OH)D status in SLE and control patients.

25(OH)D levels	SLE patients ($n = 50$)		Control ($n = 30$)		*P*-value
	N (%)	Mean ± SD	*N* (%)	Mean ± SD	
Deficiency (< 25 nmol/l)	18 (36%)	19.1 ± 9.5	5 (16.7%)	22.9 ± 6.7	< 0.001
Insufficiency (25–75 nmol/l)	32 (64%)	28.1 ± 2.7	17 (57%)	35.6 ± 5.5	0.010
Overall 25(OH)D levels	50 (100%)	26.3 ± 5.58	22 (73%)	30.7 ± 4.68	< 0.001

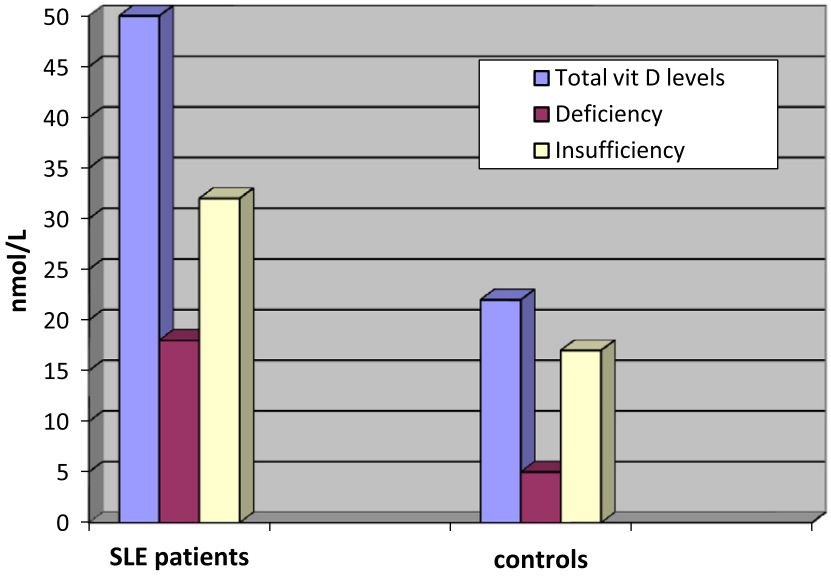

Figure 1 25(OH)D deficiency and insufficiency status in SLE and control patients.

Table 3 Cardiovascular risk factors in 25(OH)D deficient and insufficient patients.

	25(OH)D total levels ($N = 50$)	25(OH)D deficiency ($N = 18$)	25(OH)D insufficiency ($N = 32$)	P-value
DBP (mean ± SD)	87.4 ± 9.5	88.6 ± 10.4	80 ± 4.5	0.011
FBS (mean ± SD)	92.9 ± 16.5	102.3 ± 20.9	87.6 ± 10.7	< 0.001
BMI (mean ± SD)	25.8 ± 6.4	30.1 ± 6.2	23.4 ± 5.2	< 0.001
SLEDAI score (mean ± SD)	17.5 ± 8.3	22.9 ± 10	14.5 ± 5.5	0.006
SLICC score (mean ± SD)	0.56 ± 0.9	1.0 ± 1.2	0.31 ± 0.6	0.003
Cholesterol (mean ± SD)	194.4 ± 63.6	217.5 ± 60.2	174.4 ± 65.7	< 0.001
TG (mean ± SD)	188.2 ± 65.6	199.3 + 61.1	164.4 + 52.9	< 0.001
HDL (mean ± SD)	61.2 ± 15.0	52.31 ± 15.9	63.0 ± 13.4	0.074
LDL (mean ± SD)	142.2 ± 33.6	157.7 ± 32.	126.4 ± 35.3	0.005
ACL IgG IgM +ve	9 (18%)	1 (5.6%)	8 (25%)	0.087
LAC +ve	7 (14%)	1 (5.6%)	6 (18.8%)	0.197
CVS, *n* (%)	3 (6%)	2 (11.1%)	1	0.133
Subclinical markers of CVD				
RT CA IMT (mean ± SD)	3.4 ± 0.9	4.1 ± 1.5	3.0 ± 0.8	0.002
LT CA IMT (mean ± SD)	3.8 ± 1.3	4.2 ± 1.9	3.1 ± 1	0.010
RT CA stenosis, *n* (%)	5 (10%)	5 (27.8%)	0	0.006
LT CA stenosis, *n* (%)	4 (8%)	3 (16.7%)	1 (3.1%)	0.127
RT CA plaque, *n* (%)	4 (8%)	4 (22.2%)	0	0.013
LT CA plaque, *n* (%)	2 (4%)	2 (11.1)	0	0.125

Table 4 Predictive factors of low 25(OH)D.

Significant predictors	OR (95% CI)	P-value
BMI	0.83 (0.78, 0.88)	< 0.001
DBP	0.70 (0.58, 0.84)	< 0.001
Cholesterol	0.70 (0.63, 0.78)	< 0.001
Triglyceride	0.66 (0.55, 0.79)	< 0.001
LDL	0.62 (0.46, 1.12)	0.002
DM	0.59 (0.47, 0.76)	0.003

BMI: bone mineral density; DBP: diastolic blood pressure; LDL: low density lipoprotein; DM: diabetes mellitus.

In addition, our study concluded that lower vitamin D levels were associated with higher BMI, diastolic blood pressure, LDL cholesterol, triglycerides and self reported hypertension and DM using stepwise regression analysis.

It is not clear why BMI abrogates most of the relationships between CVD risk factors and 25(OH)D. One explanation may be that BMI acts as a mediator between the two by contributing to the inflammatory load of women with SLE. No significant relationship was found between cerebrovascular events and 25(OH)D levels in this study, but the number of events was too few to consider this an accurate assessment. We did however, look at the relationship between 25(OH)D levels and markers of subclinical atherosclerosis (plaque and IMT). This is important because the presence or extent of carotid plaque, increased IMT have been found to predict risk of cardio-

vascular events including myocardial infarction [27] similarly increased IMT and carotid plaques have been found to predict risk of angina and stroke in the general population [31].

In agreement with this data, our study found a significant positive correlation between 25(OH)D and the RT carotid artery stenosis and RT carotid artery plaque, in addition a positive correlation was found between 25(OH)D and the intima media thickness of both left and right carotid arteries.

We also found that lower 25(OH)D levels were associated with increased lupus disease activity and damage indices which is consistent with most other studies [12]. This is important because vitamin D have a beneficial role in preventing or attenuating some manifestations of SLE. In fact, treatment with various levels of 1,25(OH)2D3 in animal models of lupus reduced dermatologic lesions of lupus such as alopecia, in addition to proteinuria and serum anti-ds-DNA antibodies [12]. On the other hand Ruiz-Irastorza et al. [6] stated that treatment with vitamin D3 reduces fatigue in SLE patients as measured by 0–10 VAS but does not affect SLE activity or damage index.

Our study concluded a positive significant correlation between 25(OH)D and cholesterol, triglycerides and LDL levels which shows that cholesterol and triglycerides acted as a predictive factors for vitamin D deficiency which further emphasizes that lipid profile is considered a major CVD risk factor in women with SLE.

Also our study showed a positive correlation between 25(OH)D levels and proteinuria and C3 levels, this may be an important factor as 1-hydroxylation is essential to make 25-OH vitamin D active which can be disrupted in significant renal disease, we did not find a significant relationship between the glomerular filtration rate (GFR) and the level of 25(OH)D which may be related to the limited number of patients.

As regards the medications used, our study showed a significant negative correlation between 25(OH)D and the duration of steroid use and its cumulative dose while there was no correlation with the other medications given including hydroxychloroquine and other immunosuppressants. Chronic steroid use may result in altered metabolism of vitamin D, although there is contradictory evidence [26]. Dihydroxy-vitamin D3 has been demonstrated to be reduced in corticosteroid-treated patients with a variety of collagen vascular diseases and rheumatoid arthritis [32]. In rat models, steroids have been demonstrated to alter vitamin D metabolism, leading to the formation of more polar, biologically inactive metabolites that result in decreased intestinal calcium absorption [33]. The data on whether corticosteroids are pro or antiatherogenic are controversial, but some suggest that the progression of subclinical atherosclerosis based on serial carotid ultrasound correlates with lower mean dose of steroids and less aggressive immunosuppressive therapy [34]. However, corticosteroid use has also been associated with higher IMT and frequency of carotid plaque in patients with rheumatoid arthritis, and it is thought to increase the catabolism of vitamin D, thus lowering serum levels [35].

The data on the effects of hydroxychloroquine on vitamin D are also controversial [36]. Hydroxychloroquine is suspected to inhibit the conversion of 25(OH)D to its more biologically active form, 1,25-dihydroxy vitamin D, but also had been found to protect against vitamin D deficiency [37]. In terms of cardiovascular effects, hydroxychloroquine has been shown to be protective against thrombosis and cardiac disease [35].

A limitation of our study was the small number of patients, which needs to be further evaluated in large cohort of patients to determine the protective effect of adequate vitamin D levels on the development of SLE.

In conclusion, our study found an association between lower 25(OH)D levels and increased CVD risk factors, as well as increased SLE disease activity and damage indices, also with the presence of proteinuria, low complement levels and steroid use.

The physiologic and clinical effects of using vitamin D to modulate SLE disease activity and damage are not known nowadays, and there are currently no prospective studies looking at the effects of vitamin D supplementations in SLE. However, future studies are needed to determine whether vitamin D levels can predict the progression of subclinical atherosclerosis as measured by imaging markers as well as cardiovascular events in patients with lupus.

Conflict of Interest

The authors have no conflict of interest.

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