

RESEARCH

Open Access



Vitamin D in active systemic lupus erythematosus and lupus nephritis: a forgotten player

Marwa K. Khairallah^{1*} , Yasmine S. Makarem² and Marwa A. Dahpy³

Abstract

Background: Systemic lupus erythematosus (SLE) is an autoimmune disorder associated with immunological abnormalities (Aringer et al., *Arthritis Rheumatol* 71:1400-1412, 2019). Vitamin D (VD) has an important role in SLE pathogenesis, as it controls cell cycle progression besides its anti-proliferative effects (Liu et al., *J Cell Commun Signal* 71, 2019). Determining the relationship between VD with SLE activity and lupus nephritis (LN) can establish a new role for VD in SLE management (Liu et al., *J Cell Commun Signal* 71, 2019). In our study, we aimed to assess the relationship between levels of VD in patients with SLE activity and with LN and to verify the relationship between VD levels with clinical and laboratory parameters in those patients, in order to assess the validity of adding serum VD level in the routine follow-up as a marker that may lead to earlier diagnosis of SLE activity and LN in adult SLE patients.

Results: Serum VD was significantly lower in SLE patients (3.38 ± 2.55 ng/ml) versus healthy controls (5.36 ± 2.88 ng/ml) ($P < 0.002$). Interestingly, serum VD was significantly lower in patient with active SLE according to SLEDAI (3.00 ± 2.27 ng/ml) versus those with inactive SLE (5.10 ± 3.19 ng/ml) ($P < 0.02$). Significant negative correlation was found between serum level of VD and each of mucocutaneous, malar rash, and renal manifestations. Significant negative correlation was also noticed among SLEDAI (P value = 0.01) and renal SLEDAI scores (P value = 0.021) with serum level of VD.

Conclusion: Low levels of VD were found to be frequent in SLE patients especially during phases of SLE activity and nephritis. Potent markers of low serum VD level in SLE patients were found to be mucocutaneous, malar rash, and LN. Our results support that VD levels could act as independent risk factors for activity and LN in SLE patients; moreover, treatment with VD supplementation could decrease the incidence of activity and nephritis in SLE patients.

Keywords: SLE, Lupus nephritis, Vitamin D

Background

The systemic lupus erythematosus (SLE) is an inveterate immunological disorder that is characterized by abnormal inflammatory processes affecting numerous systems [1]. Recent studies postulate that aberrant apoptosis and/or necrosis encountered in SLE result from exposure of the immune system to nuclear antigens and

uptake of immune complexes by dendritic cells causing activation of interferon type-I overexpression [2]. The resulting inflammatory process leads to the development of T cells into pro-inflammatory pathways and thus producing autoantibodies [3].

Vitamin D (VD) is considered to be one of the most important lipid-soluble vitamins. It has an important role in phosphorus and calcium homeostasis and mineralization of bone [3]. After the conversion of 7-dehydrocholesterol into pre-VD3 in the skin, the body utilizes VD in addition to the smaller amounts of VD that come from the diet [4]. The

* Correspondence: Marwa.kamal82@hotmail.com

¹Nephrology Unit, Internal Medicine Department, Faculty of Medicine, Assiut University Hospital, Assiut University, Assiut, Egypt
Full list of author information is available at the end of the article

major circulating form of VD is 25-hydroxycholecalciferol (25(OH)D); thus, the total serum 25(OH)D level is currently considered the best indicator of VD supply to the body from cutaneous synthesis and nutritional intake [2]. Recently, it has been found that multiple immune cells express VD receptors (VDRs) on their surfaces [5], and several immune cells synthesize 1 α -hydroxylase enzyme needed for the synthesis of an active form of VD in lymph tissues [6]. These results suggest that VD is implicated in immune modulation [7, 8]. Several researchers tried to identify possible relations between VD and SLE. Commonly, fatigue, psychological symptoms, and musculoskeletal disorders are associated with SLE, as well as low serum VD [9]. On the contrary, other researches claimed no association between active SLE and VD levels [10].

Systemic lupus erythematosus clinical aspects are variable and target renal, respiratory, dermatological, and musculoskeletal systems [11]. Lupus nephritis occurs in about 50% of SLE patients. Active LN can be the first manifestation in ~ 30% of the patients [11], and 10–30% of SLE patients may present with renal failure within 10 years [12]. Impaired renal function can intervene with 1-hydroxylation that is important to produce active VD [8, 13]. We aimed to assess the relationship between levels of VD in SLE patients with and without activity and specially LN and to determine the relationship among VD levels, laboratory, and clinical findings in those patients.

Methods

The current study is a cross-sectional, prospective observational study that was carried out at the Nephrology Unit in the Internal Medicine department and Rheumatology, Rehabilitation, and Physical Medicine department in collaboration with the Medical Biochemistry department at Faculty of Medicine, Assiut University, during the period from January 2018 to January 2020. The study was carried out on 100 Egyptian SLE patients. All were diagnosed according to Systemic Lupus International Collaborating Clinics (SLICC) [14]. Sixty-six healthy age- and sex-matched controls were enrolled in the study. A written consent to participate in the study was signed by each participant. The study was approved by the Institutional Review Board of Faculty of Medicine (IRP No. 17300432).

We included patients older than 18 years suffering from SLE who fulfilled four or more criteria (at least one clinical and one laboratory criterion) or biopsy-proven LN with positive antinuclear antibodies or anti-DNA according to SLICC, while patients with other systemic autoimmune diseases and/or with urinary tract infection ($\geq 100,000$ colony-forming units in urine culture) and those undergoing hemodialysis or with a history of renal transplantation were excluded from the study.

All participants were subjected to clinical assessment through full history taking, systemic, and local examinations. The following parameters were recorded: age, sex, duration of SLE, photosensitivity, skin changes, active arthritis, LN, and history of drug intake [steroids, hydroxychloroquine, calcium, and VD supplements]. The following laboratory investigations performed include: urine analysis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum creatinine, ALT, C3, C4 concentrations, creatine phosphokinase (CPK), presence of anti-nuclear auto-antibodies (ANA) and the anti-ds-DNA, 24-h protein in urine, and lipid profile including serum cholesterol, serum triglycerides, low-density lipoproteins, and high-density lipoproteins.

The assessment of SLE activity was determined according to the modified SLE disease activity index (SLEDAI) score with higher scores representing increased activity [15], while LN was assessed by renal SLEDAI [16].

In our study, SLE patients were classified as follows: (i) active SLE: SLEDAI score of 8 or more (82 patients), (ii) inactive SLE: SLEDAI score of less than 8 (18 patients), (iii) lupus nephritis patients (68 patients), (iv) SLE patients without nephritis (32 patients).

The sample size was determined in accordance with SLEDAI scores in both active SLE and LN. The calculated minimum sample size was 100 SLE patients.

Assessment of vitamin D

Serum 25-hydroxycholecalciferol VD (25(OH)D) was measured by using Abcam ELISA Kit catalog number ab213966. Insufficient VD was estimated at levels < 30 ng/mL and deficiency at < 10 ng/mL. We considered any level of VD < 30 ng/mL a low value for statistical purposes.

Statistical analysis

Statistical analysis was done by utilizing statistical Package Social Sciences version 20.0 (SPSS). Continuous data were expressed as mean \pm standard deviation (SD), but categorical data were expressed in percentages and numbers. Differences between groups were determined using the chi-square test for categorical data or *T* test for continuous data. Correlation between different variables was performed. The receiver operating characteristic (ROC) curve was performed for calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. Statistical significance was defined as a *P* value < 0.05.

Results

In our current study, systemic lupus erythematosus group included 88 females (88%) and 12 males (12%), and their disease duration ranged from 0.5 to 12.0 years with a mean \pm SD of 4.0 \pm 3.2 years. The 66 healthy

controls included 58 females (87.87%) and eight males (12.12%), with mean age ± SD of 25.32 ± 6.98 with a range of 18.0–51.0 years. There was no significant difference among the patients and the control group regarding age and sex (Table 1).

Comparing the laboratory findings between SLEDAI ≥ 8 and SLEDAI < 8 groups, our results revealed that SLEDAI ≥ 8 group had significantly lower values of CPK (68.88 ± 30.08) (*P* = 0.03), C4 (2.06 ± 1.21) (*P* = 0.000), and 25(OH)VD (3.00 ± 2.27) (*P* = 0.02) compared to SLEDAI < 8 group (Table 2).

As for the comparison between renal SLEDAI groups, levels of CPK (68.29 ± 27.64) (*P* = 0.02), serum albumin (36.03 ± 7.63) (*P* = 0.04), and 25(OH)VD (ng/ml) (2.58 ± 1.82) (0.003) in positive renal SLEDAI group are significantly lower than in negative renal SLEDAI group. A significant increase in the levels of ALP (84.88 ± 63.78) (*P* = 0.03) and 24-h urinary proteins (mg) (1581.81 ± 1886.05) (*P* = 0.003) was significantly higher in positive renal SLEDAI group versus negative renal SLEDAI group. None of the negative renal SLEDAI group had pus in the urine, hematuria mean while 64.7%; 55.9% of the positive renal SLEDAI had pus in the urine and hematuria respectively (Table 3).

Table 1 Demographic and laboratory data of SLE patients and control group

Variables	SLE (n = 100)	Control (n = 66)	P value
Age (years)			
Mean ± SD	28.30 ± 8.9	25.32 ± 6.98	0.93
Range	(19.0–54.0)	(18.0–51.0)	
Sex			
Male	12 (12%)	8 (12.12%)	0.99
Female	88 (88%)	58 (87.87)	0.89
Duration of disease			
Mean ± SD	4.0 ± 3.2		
Range	(0.5–12.0)		
ANA			
negative	14 (14%)	66 (100%)	0.000*
positive	86 (86%)	0	
Anti-dsDNA	2.00 ± 1.57	0.25 ± 0.12	0.000*
C3 (ug/ml)	3.39 ± 2.92	7.06 ± 3.36	0.000*
C4 (ug/ml)	2.48 ± 1.61	4.73 ± 2.34	0.000*
25(OH)D (ng/ml)	3.38 ± 2.55	5.36 ± 2.88	0.002**

Data are presented as mean ± SD (standard deviation) or number (n) and percentage (%). The independent samples t test was used to compare between means of different parameters in SLE patients and controls. Chi-square test was used to analyze the significance between the percentages. *P* value < 0.05 is considered to be a significant value

ANA anti-nuclear auto-antibodies, Anti dsDNA anti-double strand antibody, C3 complement 3, C4 complement 4, 25(OH)D 25-hydroxyvitamin D

*Statistically significant (*P* < 0.05)

**Moderately statistically significant (*P* < 0.01)

Interestingly, we found no significant differences in 25(OH)VD levels between patients taking hydroxychloroquine and those not, where 25(OH)VD levels were 3.41 ± 2.63 ng/ml in patients taking hydroxychloroquine and 3.13 ± 2.11 ng/ml in those who were hydroxychloroquine free. In addition, we found that serum 25(OH)VD levels were not significantly different among patients taking steroids (3.51 ± 2.73 ng/ml) and those who were steroid-free (2.65 ± 1.19 ng/ml) (Table 4).

In our current study, significant negative correlations between levels of serum 25(OH)VD and clinical findings in studied SLE patients, including mucocutaneous, malar rash, and renal symptoms, also, there was significant negative correlation between 25(OH)VD level and both SLEDAI and renal SLEDAI scores. Importantly, serum 25(OH)VD showed no significant correlation with C3, C4, serum creatinine, and other clinical and lab results in SLE patients (Table 5).

Multiple logistic regression analysis showed that the most potent parameters determining low levels of serum 25(OH)VD were higher SLEDAI score (*p* = 0.002) and lower C3 (*p* = 0.035) (Table 6).

To quantify the utility of 25(OH)VD in determining the activity in SLE patients, analysis by ROC curve of 25(OH)VD for SLEDAI and renal SLEDAI is shown in Fig. 1, where the sensitivity and specificity were 73.2% and 77.8%, respectively; positive predictive value (PPV) and negative predictive value (NPV) were 93.7% and 38.9%, respectively; and 74.0% accuracy at cutoff point < 2.5 with an area under curve (AUC) 0.748. Besides, our study also showed that 25(OH)VD at cutoff point < 2.2 ng/ml had a sensitivity and specificity of 64.7% and 93.8% respectively, PPV and NPV are 95.7% and 55.6% respectively, and 74.0% accuracy (Fig. 1).

Discussion

Measurement of circulating 25(OH)VD is considered the best indicator of VD status in humans, as it represents VD stores gained from both dietary intake and ultraviolet light [17]. Despite the certainty of the presence of sunny days most of the year in Egypt, the present study proposes that VD deficiency is widely predominant in patients with active SLE and LN in Egypt, this is in accordance with Elsaid et al. who found that the prevalence of VD deficiency and insufficiency in LN patients is as high as 93.4% in Egyptian patients [18]. Our study results also were in agreement with Korah et al. who found that Egyptian SLE patients had lower VD levels in comparison to healthy controls [19]. Additionally, our study showed that low VD levels could act as an independent risk factor for SLE activity where the mean concentration of VD was significantly lower in SLEDAI score ≥ 8 (3.00 ± 2.27 ng/ml) versus in SLEDAI score < 8 (5.10 ± 3.19 ng/ml). These findings documented low

Table 2 Comparison between SLEDAI groups regarding the laboratory tests

Variable	SLEDAI < 8 "n = 18"	SLEDAI ≥ 8 "n = 82"	P value
ESR (mm/1st h)	40 ± 29.82	49.54 ± 30.97	0.93
CRP (mg/L)	9.02 ± 15.71	11.21 ± 18.56	0.83
Hb (g/dl)	11.22 ± 1.16	10.87 ± 1.63	0.55
RBCs (10 ³ /μl)	3.90 ± 0.90	4.27 ± 0.69	0.18
WBCs (10 ³ /μl)	5.30 ± 2.42	5.26 ± 2.35	0.96
Platelets (10 ³ /μl)	286.33 ± 100.18	280.34 ± 114.63	0.88
AST (U/L)	22.56 ± 9.40	23.92 ± 8.79	0.83
ALT (U/L)	25.11 ± 16.51	19.44 ± 3.47	0.47
ALP (IU/L)	87.33 ± 15.85	73.59 ± 53.79	0.50
CPK (U/L)	133.89 ± 64.09	68.88 ± 30.08	0.03*
LDH (U/L)	289.44 ± 94.65	321.39 ± 136.55	0.51
Serum albumin (g/dl)	40.12 ± 4.01	37.50 ± 7.85	0.34
A/G ratio	1.24 ± 0.311	1.16 ± 0.35	0.53
Glucose (mmol/L)	4.88 ± 1.13	5.71 ± 1.02	0.71
Urea (mmol/L)	4.20 ± 1.36	6.15 ± 0.73	0.23
Creatinine (μmol/L)	49.80 ± 14.34	80.66 ± 20.29	0.48
Serum TC(mg/dl)	151.55 ± 31.33	172.12 ± 46.56	0.21
serum TG(mg/dl)	109.00 ± 46.48	140.39 ± 17.40	0.48
HDL-c (mg/dl)	40.97 ± 7.45	45.64 ± 17.03	0.43
LDL-c (mg/dl)	88.11 ± 23.08	98.11 ± 42.79	0.50
Creatinine Clearance (ml/min)	86.24 ± 38.95	103.43 ± 45.41	0.30
24 h protein in urine (mg)	723.04 ± 272.82	1275.0 ± 278.89	0.37
Pus/HPF in urine			
negative	7(77.8%)	21(51.2%)	0.14
positive	2(22.2%)	20(48.8%)	
RBCs in urine			
negative	7(77.8%)	24(58.5%)	0.25
positive	2(22.2%)	17(41.5%)	
Urinary cast			
negative	8(88.9%)	37(90.2%)	0.65
positive	1(11.1%)	4(9.8%)	
Crystals in urine			
negative	7(77.8%)	36(87.8%)	0.37
positive	2(22.2%)	5(12.2%)	
Albumin in urine			
negative	6(66.7%)	23(56.1%)	0.42
positive	3(33.3%)	18(43.9%)	
C3 (μg/ml)	4.77 ± 2.16	3.09 ± 2.36	0.119
C4 (μg/ml)	4.40 ± 1.88	2.06 ± 1.21	0.000***
Anti-dsDNA	1.34 ± 1.20	2.14 ± 1.62	0.170
25(OH)D (ng/ml)	5.10 ± 3.19	3.00 ± 2.27	0.02*

Data are presented as numbers (n) and mean ± SD (standard deviation). The independent samples t test was used to compare between means of different parameters in SLEDAI groups. P value < 0.05 is considered to be a significant value

SLEDAI systemic lupus erythematosus disease activity index, ESR erythrocyte sedimentation rate, CRP C- reactive protein, Hb hemoglobin, RBCs red blood cells, WBCs white blood cells, AST aspartate transaminase, ALT alanine transaminase, ALP alkaline phosphatase, CPK creatinine phosphokinase, LDH lactate dehydrogenase, A/G ratio albumin globulin ratio, TC total cholesterol, TG triglyceride, HDL high-density lipoproteins, LDL low-density lipoproteins, HPF high power field, C3 complement 3, C4 complement 4, Anti-dsDNA anti-d double-stranded deoxyribonucleic acid, 25(OH)D 25 hydroxyvitamin D

*Statistically significant (P < 0.05)

***Highly statistically significant (P < 0.001)

Table 3 Comparison between renal SLEDAI groups regarding the laboratory tests

Variable	Renal SLEDAI (negative) "n = 32"	Renal SLEDAI (positive) "n = 68"	P value
AST (U/L)	21.56 ± 9.05	24.67 ± 20.23	0.43
ALT (U/L)	18.75 ± 12.57	21.26 ± 24.50	0.4
ALP (IU/L)	57.31 ± 14.79	84.88 ± 63.78	0.03*
CPK (U/L)	106.69 ± 146.50	68.29 ± 27.64	0.02*
LDH (U/L)	286.69 ± 71.40	329.26 ± 148.62	0.09
Serum albumin (g/dl)	42.13 ± 4.61	36.03 ± 7.63	0.04*
A/G ratio	1.32 ± 0.39	1.11 ± 0.30	0.42
Glucose (mmol/L)	5.08 ± 1.57	5.80 ± 7.14	0.4
Urea (mmol/L)	4.69 ± 1.88	6.32 ± 5.04	0.08
Creatinine (µmol/L)	48.4 ± 16.08	87.68 ± 141.82	0.15
Serum total cholesterol (mg/dl)	167.25 ± 35.43	168.97 ± 48.88	0.41
Triglyceride (mg/dl)	136.06 ± 131.44	134.12 ± 89.17	0.89
HDL-C (mg/dl)	47.85 ± 14.31	43.38 ± 16.44	0.48
LDL-C(mg/dl)	90.11 ± 40.73	99.24 ± 39.87	0.97
Creatinine Clearance (ml/min)	93.97 ± 40.15	103.33 ± 46.61	0.87
24 h protein in urine (mg)	312.43 ± 129.10	1581.81 ± 1886.05	0.003**
Pus/HPF in urine			0.002**
negative	16 (100%)	12 (35.3%)	
positive	0 (0%)	22 (64.7%)	
RBCs in urine			0.001**
negative	16 (100%)	15 (44.1%)	
positive	0 (0%)	19 (55.9%)	
Urinary cast			0.13
negative	16 (100%)	29 (85.3%)	
positive	0 (0%)	5 (14.7%)	
Crystals in urine			0.27
negative	15 (93.8%)	28 (82.4%)	
positive	1 (6.2%)	6 (17.6%)	
Albumin in urine			0.004**
negative	14 (87.5%)	15 (44.1%)	
positive	2 (12.5%)	19 (55.9%)	
C3 (µg/ml)	3.74 ± 2.67	3.23 ± 3.06	0.963
C4 (µg/ml)	3.05 ± 2.22	1.83 ± 1.45	0.098
Anti-dsDNA	1.52 ± 1.34	2.22 ± 1.65	0.987
25(OH)D (ng/ml)	5.07 ± 3.10	2.58 ± 1.82	0.003***

Data are presented as mean ± SD. The independent samples t test was used to compare between means of different parameters in SLEDAI groups. P value < 0.05 is considered to be a significant value

SD standard deviation, SLEDAI systemic lupus erythematosus disease activity index, AST aspartate transaminase, ALT alanine transaminase, ALP alkaline phosphatase, CPK creatinine phosphokinase, LDH lactate dehydrogenase, A/G ratio albumin globulin ratio, TC total cholesterol, TG triglyceride, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, HPF high power field, C3 complement 3, C4 complement 4, Anti-dsDNA anti-d double-stranded deoxyribonucleic acid, 25(OH)D 25 hydroxyvitamin D

*Statistically significant (P < 0.05)

**Moderately statistically significant (P < 0.01)

***Highly statistically significant (P < 0.001)

Table 4 Comparison between steroids, hydroxychloroquine, calcium, and VD supplements with anti-ds DNA and 25(OH)D

	HQ (negative) "n = 12"	HQ (positive) "n = 88"	P value	Steroids (negative) "n = 16"	Steroids (positive) "n = 84"	P value	Calcium and VD (negative) "n = 74"	Calcium and VD (positive) "n = 26"	P value
Anti-dsDNA	2.71 ± 1.28	1.90 ± 0.99	0.24	2.37 ± 1.98	1.93 ± 1.19	0.24	2.12 ± 1.68	1.63 ± 1.23	0.34
25(OH)D	3.13 ± 2.11	3.41 ± 2.63	0.80	2.65 ± 1.19	3.51 ± 2.73	0.97	2.13 ± 1.04	6.92 ± 2.25	0.000***

Data are presented as mean ± SD. The independent samples t test was used to compare between means of different parameters. P value < 0.05 is considered to be a significant value

HQ hydroquinone, Anti-dsDNA anti-d double stranded deoxyribonucleic acid, 25(OH)D 25 hydroxyvitamin D

***Highly statistically significant (P < 0.001)

VD levels among Egyptian individuals especially in SLE patients despite the effect of high-ultraviolet seasons most of the year which could be explained by conventional clothing that frequently decreases their exposure to the sun [20].

There is conflicting evidence regarding the effect of chronic use of corticosteroids on VD metabolism [21]. A previous study showed that corticosteroid intake was inversely associated with serum 25(OH)D3 [22]. On the contrary, our study found no significant differences in 25(OH)VD levels between patients taking corticosteroids and those who were not taking corticosteroids; this finding was in agreement with Mazziotti et al.'s results that explained this finding by the fact that usage of low-dose of corticosteroids (10 mg/d prednisolone equivalent) have no effect on VD levels [23].

As for the effect of antimalarial drug on VD level, our study did not show a significant difference in serum 25(OH)D3 level between those who take anti-malarial treatment and those who do not. It is well-known that hydroxychloroquine is considered an important drug in SLE management; however, it was suspected to decrease the conversion of 25(OH)D3 to more biologically active 1,25(OH)2D3 [22]. In agreement with our results, recent studies found that serum 25(OH)D3 levels in SLE patients are not altered by taking hydroxychloroquine [24, 25]. Still, further studies are needed as the majority of our patients are taking antimalarial treatment.

Our study showed that VD supplementation is comparatively safe and significantly increases the levels of serum 25(OH)VD in patients with SLE, even though, VD supplements do not appear to significantly decrease the positivity of anti-dsDNA and SLE activity (Table 4), this is in agreement with Zheng et al. [26]. Another interesting observation in our study is the inverse correlation between serum levels of VD and clinical symptoms in SLE patients including mucocutaneous, malar rash, and renal symptoms. However, our study showed no correlation between VD levels and fatigue in SLE patients; our finding is consistent with Fragoso et al. who also revealed no significant association between VD levels and fatigue in SLE patients [10], but our

observation was different from that of Stockton et al., who observed a significant correlation between fatigue and VD levels in SLE [27]. This discrepancy could be explained as blood VD levels do not indicate the amount of VD stored in body tissues [28]. Moreover, recent reviews discussed the association between serum VD levels and clinical data in SLE patients including fatigue and documented the presence of several controversies regarding the association of VD levels and fatigue [9, 29].

There are variable interesting observations in the present study that suggest the presence of a serious function for vitamin D3 in disease modulation. Our results revealed that serum VD level had a significant negative correlation with SLEDAI score in both active SLE and LN. This could be explained by the potential role of vitamin D in the immune system [30]. It was proposed that immune cells as T cells, B cells, dendritic cells, and macrophages, which express VD receptors, can be promoted by adequate VD supplements. Additionally, several autoimmune disorders are associated with low VD levels [7]. In agreement with our results, various past studies showed a potent negative correlation between SLEDAI score and VD levels [18, 31, 32]. Moreover, systemic lupus erythematosus patients with severe VD deficiency were found to have significantly more SLE flares and nephritis [33]. This observed significant negative correlation between SLE activity and VD level in our study could be predicted as VD catabolic process is enhanced by the underlying inflammation in lupus [34]. Still the association between VD level and SLEDAI scores has not been uniform across observations where several studies have found none [35, 36].

Another interesting observation in the current study is the absence of correlation between 25(OH)VD with laboratory investigation including, C3 ($r = -0.153, P = 0.288$), C4 ($r = 0.177, P = 0.22$), and anti-dsDNA ($r = -0.136, P = 0.345$); these findings were matched with those of Mok et al. [37]. In disagreement with our study, Mandal et al. found that the plasma level of 25-OH VD was negatively correlated with anti-dsDNA ($r = -0.39, P < 0.0001$) [38]; also, Bonakdar et al. and Nerviani et al. found a significant correlation between VD deficiencies with anti-dsDNA, lower serum

Table 5 25(OH)VD correlations with clinical data, laboratory investigations, SLEDAI, renal SLEDAI, and immunological parameters

Variable	25(OH)D <i>r</i> value	25(OH)D <i>P</i> value
Fatigue	0.002	0.99
Fever	- 0.131	0.28
Mucocutaneous	- 0.234	0.05*
Alopecia	- 0.189	0.12
Malar rash	- 0.287	0.02*
Ulcer	- 0.082	0.50
Musculoskeletal	0.8	0.50
Myositis	0.92	0.44
Arthritis	- 0.016	0.89
Neuropsychiatric	- 0.082	0.50
Vasculitis	- 0.078	0.52
Renal	- 0.43	0.000***
Serositis	- 0.168	0.16
ESR	- 0.144	0.31
CRP	- 0.088	0.54
HB	0.141	0.32
RBCs	- 0.050	0.72
WBCs	- 0.064	0.65
PLT	0.095	0.51
ALT	- 0.004	0.97
AST	0.014	0.92
ALP	- 0.061	0.67
CPK	0.114	0.43
LDH	- 0.196	0.17
Serum albumin	0.189	0.19
A/G ratio	0.198	0.17
Glucose	- 0.105	0.47
Urea	- 0.199	0.17
Creatinine	- 0.123	0.4
Cholesterol	- 0.117	0.42
Triglyceride	- 0.049	0.74
HDL	- 0.056	0.7
LDL	- 0.094	0.52
Creatinine clearance	- 0.065	0.65
24 h protein in urine	- 0.170	0.24
SUA	- 0.199	0.17
ANA	0.142	0.24
SLEDAI	- 0.361	0.01*
Renal SLEDAI	- 0.325	0.02*
C3	- 0.153	0.288
C4	0.177	0.22
Anti-dsDNA	- 0.136	0.345

Data shown are Pearson's correlation coefficient (*r*) and *p* values. Significant correlations are highlighted in bold letters and shown as *P* value < 0.05 is a significant value

**Statistically significant (*P* < 0.05)

***Highly statistically significant (*P* < 0.001)

Table 6 Multiple regression analysis to assess the most affected parameters with 25(OH)VD deficiency

Variable	Beta	<i>P</i> value
SLEDAI score	- 0.455	0.002**
C3	- 0.297	0.035**

P value < 0.05 is considered to be a significant value

SLEDAI systemic lupus erythematosus disease activity index, C3 complement 3

**Moderately statistically significant

albumin, higher levels of liver enzymes, and higher hemoglobin concentrations [39, 40]. This controversy could be attributed to the immunosuppressive effect of the corticosteroids taken by 84% of our patients.

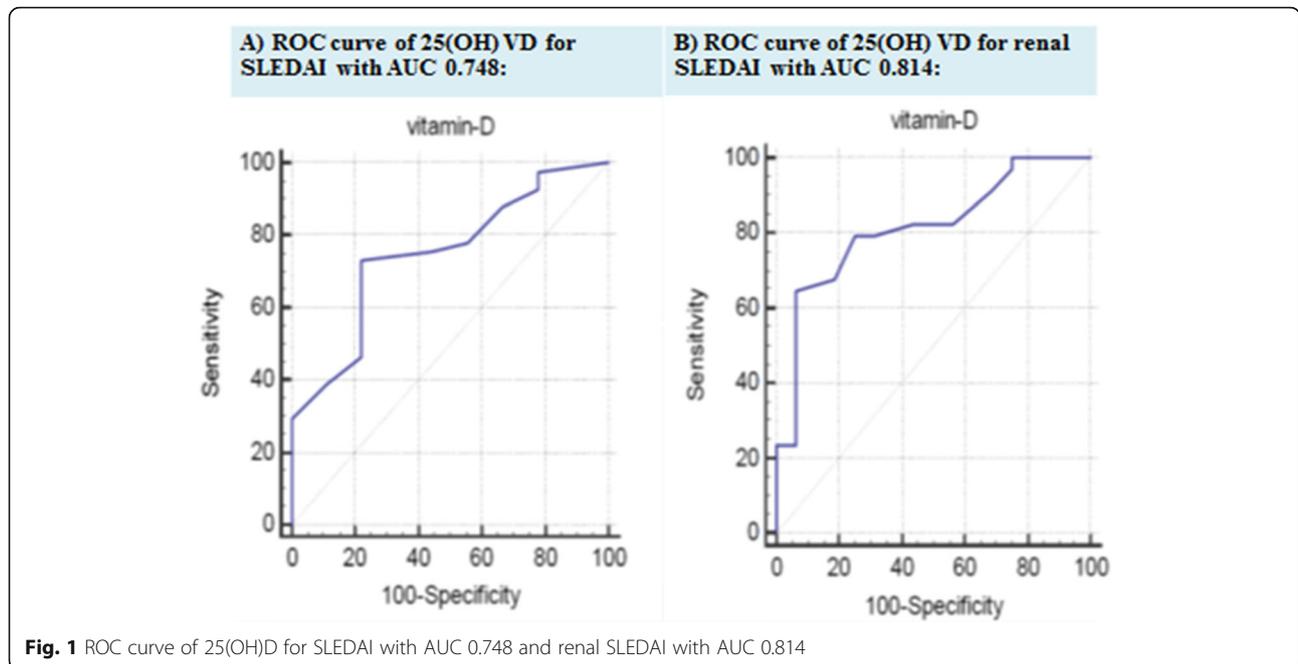
The present study showed no significant association between VD levels with ESR and CRP; this is in agreement with several studies that also did not find this association [5, 25].

In the current study, we performed multiple regression analyses to explore the clinical or laboratory manifestations with the strongest association with the serum VD levels among SLE patients. Multiple regression analysis showed that the SLEDAI score and C3 complement are potent predictors for lower serum 25(OH)VD levels. In disagreement with several studies [19], our study showed no significant association between lab parameters as proteinuria and creatinine level with lower serum VD level in the regression analysis, but the value of this finding is diminished by the fact that the mean ± SD of serum creatinine in the SLEDAI scores in both active SLE and LN was 80.66 ± 20.29 and 87.68 ± 141.82, respectively. Our results showed that VD had a sensitivity and specificity of 73.2% and 77.8%, respectively, for determining SLE activity at cutoff point < 2.5 and at cutoff point < 2.2; the sensitivity and specificity were 64.7% and 93.8% respectively for determining LN; these results are in concordance with Mok et al. results [37].

Few restrictions of this study involve the small number of patients and our inability to obtain enough renal tissue from all SLE patients for histopathology, either due to contraindicated active LN thrombocytopenia or refusal of patients, so studying a larger number of populations with variable treatment protocols to confirm the association between VD with SLE activity and nephritis is recommended to confirm the findings of the present study.

Summary

The major results of the present study can be summarized in the following points: (I) Low serum VD level is an independent risk factor in active SLE those with LN. (II) Low VD level is associated with mucocutaneous, malar rash, and renal symptoms. (III) VD is inversely correlated with SLEDAI and renal SLEDAI scores.



Conclusion

Vitamin D deficiency is common in patients with SLE especially in LN and in SLE with SLEDAI score ≥ 8 patients. Low serum VD is significantly associated with higher SLEDAI and renal SLEDAI scores. The presence of mucocutaneous, malar rash, and renal symptoms are significantly correlated with VD deficiency. Higher SLEDAI scores and lower C3 are the strongest predictors of low serum VD levels among SLE patients. Finally, adding VD level as a marker to routine follow-up may result in earlier diagnosis of SLE activity and LN in adult SLE patients.

Abbreviations

ALT: Alanine aminotransferase; ANA: Anti-nuclear auto-antibodies; Anti-DNA: Anti-double strand antibody; AST: Aspartate transaminase; C3: Complement 3; C4: Complement 4; CPK: Creatine phosphokinase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; Hb: Hemoglobin; HDL: High-density lipoproteins; LDH: Lactate dehydrogenase; ROC: Receiver operating characteristic curve; SD: Standard deviation; SLE: Systemic lupus erythematosus; SLEDAI: Systemic lupus erythematosus disease activity index; SLICC: Systemic Lupus International Collaborating Clinics classification criteria; VD: Vitamin D; VDRs: VD receptors; (25(OH)D): 25-hydroxycholecalciferol

Acknowledgements

I would like to express my deepest gratitude for all my co-authors and all my participants who were the cornerstone for the achievements in this research article to appear.

Authors' contributions

MKK and YSM conceived of the presented idea. MKK, YSM, and MAD developed the theory and performed the computations. MKK, YSM, and MAD verified the analytical methods. MKK, YSM, and MAD revised all the findings of this work. All authors discussed the results and contributed to the final manuscript. MKK and YSM carried out the experiment. MKK wrote the manuscript with support from MAD. MKK and MAD contributed to sample preparation. MKK and MAD contributed to the interpretation of the results. All authors provided critical feedback and helped shape the research,

analysis, and manuscript. All authors approved the submitted version. All authors agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. All authors have read and approved the manuscript.

Funding

Authors declare that they did not receive any funding to do this work.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

There was no risk during the application of the research. Privacy and confidentiality was maintained during all stages of assessment. Every patient subjected to this study was informed about the results of the research.

This study was approved by the ethics committee of Faculty of Medicine, Assiut University, with approval number 17300432. The study protocol was reviewed and approved by Medical Ethics Committee in accordance with Helsinki declaration.

Consent to participate statement:

Consent (written) was obtained from the patient to participate in this study. Refusal would not affect medical services which are usually offered.

Consent for publication

Consent for publication (written) was obtained from all the participating patients. Written consent is approved by the ethics committee.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Nephrology Unit, Internal Medicine Department, Faculty of Medicine, Assiut University Hospital, Assiut University, Assiut, Egypt. ²Department of Rheumatology and Rehabilitation, Faculty of Medicine, Assiut University,

Assiut, Egypt. ³Department of Medical Biochemistry and molecular Biology, Faculty of Medicine, Assiut University, Assiut, Egypt.

Received: 15 June 2020 Accepted: 14 August 2020

Published online: 20 October 2020

References

- Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R et al (2019) 2019 European league against rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol* 71(9):1400–1412
- Liu D, Fang YX, Wu X, Tan W, Zhou W, Zhang Y et al (2019) 1, 25-(OH) 2 D3/vitamin D receptor alleviates systemic lupus erythematosus by downregulating Skp2 and upregulating p27. *Cell Commun Signal* 17(1):163
- Liu, T., Son, M., & Diamond, B. (2020). HMGB1 in systemic lupus erythematosus. *Front Immunol*, 11. 2020; Accessed: March 11, 2020.
- Bikle DD (2014) Vitamin D metabolism, mechanism of action, and clinical applications. *Chem Biol* 21(3):319
- Miskovic R, Plavsic A, Raskovic S, Jovicic Z et al (2015) Vitamin D status in patients with systemic lupus erythematosus in Serbia: correlation with disease activity and clinical manifestations. *Open Access Maced J Med Sci* 3(2):256
- Hassanalilou T, Khalili L, Ghavamzadeh S, Shokri A, Payahoo L, Bishak YK (2018) Role of vitamin D deficiency in systemic lupus erythematosus incidence and aggravation. *Auto Immun Highlights* 9(1):1
- Murdaca G, Tonacci A, Negrini S, Greco M, Borro M, Puppo F et al (2019) Emerging role of vitamin D in autoimmune diseases: an update on evidence and therapeutic implications. *Autoimmun Rev* 18(9):102350
- Schröder-Heurich B, Springer CJP et al (2020) Vitamin D effects on the immune system from periconception through pregnancy. *Nutrients* 12(5): 1432
- Nguyen MH, Bryant K, O'Neill SG (2018) Vitamin D in SLE: a role in pathogenesis and fatigue? A review of the literature. *Lupus* 27(13):2003–2011. <https://doi.org/10.1177/0961203318796293>
- Fragoso TS, Dantas AT, Marques CD, Rocha Junior LF, Melo JH et al (2012) 25-Hydroxyvitamin D3 levels in patients with systemic lupus erythematosus and its association with clinical parameters and laboratory tests. *Rev Bras Reumatol* 52:60–65
- Almaani S, Meara A, Rovin BH (2017) Update on lupus nephritis. *Clin J Am Soc Nephrol* 12(5):825–835
- Lateef A, Petri M (2012) Unmet medical needs in systemic lupus erythematosus. *Arthritis Res Therapy* 14(S4):S4
- Franca Gois, P. H., Wolley, M., Ranganathan, D.,... & Seguro, A. C. (2018). Vitamin D deficiency in chronic kidney disease: recent evidence and controversies. *Int J Environ Res Public Health*, 15(8), 1773 D
- Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR et al (2012) Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheumatism* 64(8):2677–2686
- Gladman DD, Ibanez D, Urowitz MB (2002) Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 29(2):288–291
- Xuejing Z, Jiazhen T, Jun L, Xiangqing X, Shuguang Y, Fuyou L (2012) Urinary TWEAK level as a marker of lupus nephritis activity in 46 cases. *J Biomed Biotechnol* 2012
- Pilz S, Zittermann A, Trummer C, Theiler-Schwetz V, Lerchbaum E, Keppel MH et al (2019) Vitamin D testing and treatment: a narrative review of current evidence. *Endocrine Connect* 8(2):R27–R43
- Elsaid TO, Basma A, Nabih AA, Elewa AM (2018) Serum vitamin D in Egyptian patients with systemic lupus erythematosus and its association with lupus nephritis. *Int J Clin Rheumatol* 13(5)
- Korah TE, Soliman SG, Al-Sharaki DR et al (2013) Vitamin D in systemic lupus erythematosus patients with and without nephropathy. *Egypt Rheumatol Rehabil* 40(3):165–175
- Mostafa WZ, Hegazy RA (2015) Vitamin D and the skin: focus on a complex relationship: a review. *J Adv Res* 6(6):793–804
- Davidson ZE, Walker KZ, Truby H (2012) Do glucocorticosteroids alter vitamin D status? A systematic review with meta-analyses of observational studies. *J Clin Endocrinol Metabol* 97(3):738–744
- Ruiz-Iratorza G, Egurbide MV, Olivares N, Martinez-Berriotxo A, Aguirre C (2008) Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. *Rheumatology* 47(6):920–923
- Mazziotti G, Formenti AM, Frara S, Doga M, Giustina A (2018) Vitamin D and Glucocorticoid-Induced Osteoporosis. In: Giustina A, Bilezikian JP (ed) *Vitamin D in Clinical Medicine*. Basel: Karger; Front Horm Res 50:149–60. <https://doi.org/10.1159/000486078>
- Durcan L, Clarke WA, Magder LS, Petri M (2015) Hydroxychloroquine blood levels in systemic lupus erythematosus: clarifying dosing controversies and improving adherence. *J Rheumatol* 42(11):2092–2097
- Kim HA, Sung JM, Jeon JY, Yoon JM, Suh CH (2011) Vitamin D may not be a good marker of disease activity in Korean patients with systemic lupus erythematosus. *Rheumatol Int* 31(9):1189–1194
- Zheng R, Gonzalez A, Yue J, Wu X, Qiu M, Gui L et al (2019) Efficacy and safety of vitamin D supplementation in patients with systemic lupus erythematosus: a meta-analysis of randomized controlled trials. *Am J Med Sci* 358(2):104–114onghao
- Socketon KA, Kandiah DA, Paratz JD, Bennell KL (2012) Fatigue, muscle strength and vitamin D status in women with systemic lupus erythematosus compared with healthy controls. *Lupus* 21(3):271–278
- De la Puente Yagüe M, Collado Yurrita L, Cuadrado Cenual MA (2020) Role of vitamin D in athletes and their performance: current concepts and new trends. *Nutrients* 12(2):579
- Magro R, Borg AA (2017) The effect of vitamin D on disease activity, fatigue and interferon signature gene expression in systemic lupus erythematosus. *Mediterr J Rheumatol* 28(3):12
- Chaiamnuy S, Chailurkit LO, Narongroeknawin P, Asavatanabodee P, Laohajaroensombat S, Chaiamnuy P (2013) Current daily glucocorticoid use and serum creatinine levels are associated with lower 25 (OH) vitamin D levels in Thai patients with systemic lupus erythematosus. *JCR: Journal of Clinical Rheumatology* 19(3):121–112
- Abaza NM, El-Mallah RM, Shaaban A, Mobasher SA, Al-Hassanein KF, Zaher AAA, El-Kabarity RH (2016) Vitamin D deficiency in Egyptian systemic lupus erythematosus patients: how prevalent and does it impact disease activity? *Integrative medicine insights*, 11, IMI-S40035
- Lin TC, Wu JY, Kuo ML, Ou LS, Yeh KW, Huang JL (2018) Correlation between disease activity of pediatric-onset systemic lupus erythematosus and level of vitamin D in Taiwan: a case-cohort study. *J Microbiol Immunol Infect* 51(1):110–114
- Cutolo M, Otsa K, Paolino S, Yprus M, Veldi T, Serio B (2009) Vitamin D involvement in rheumatoid arthritis and systemic lupus erythematosus. *Ann Rheum Dis* 68(3):446–447
- Ben-Zvi I, Aranow C, Mackay M, Stanevsky A, Kamen DL, Marinescu LM et al (2010) The impact of vitamin D on dendritic cell function in patients with systemic lupus erythematosus. *PLoS One* 5(2):e9193
- Toloz SMA, Cole DEC, Gladman DD, Ibanez D, Urowitz MB (2010) Vitamin D insufficiency in a large female SLE cohort. *Lupus* 19(1):13–19
- Schoindre, Y., Jallouli, M., Tanguy, M. L., Ghillani, P., Galicier, L., Aumaitre, O., ... & Limal, N. (2014). Lower vitamin D levels are associated with higher systemic lupus erythematosus activity, but not predictive of disease flare-up. *Lupus science & medicine*.
- Mok CC, Birmingham DJ, Ho LY, Hebert LA, Song H, Rovin BH (2012) Vitamin D deficiency as marker for disease activity and damage in systemic lupus erythematosus: a comparison with anti-dsDNA and anti-C1q. *Lupus* 21(1):36
- Mandal M, Tripathy R, Panda AK, Pattanaik SS, Dakua S, Pradhan AK et al (2014) Vitamin D levels in Indian systemic lupus erythematosus patients: association with disease activity index and interferon alpha. *Arthritis Res Therapy* 16(1):R49
- Bonakdar ZS, Jahanshahifor L, Jahanshahifor F, Gholamrezaei A (2011) Vitamin D deficiency and its association with disease activity in new cases of systemic lupus erythematosus. *Lupus*. 20(11):1155–1160
- Nerviani, A., Mauro, D., Gilio, M., Grembale, R. D., & Lewis, M. J. (2018). To supplement or not to supplement? The rationale of vitamin D supplementation in systemic lupus erythematosus. *Open Rheumatol J*, 12(1).

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.