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Effect of Vitamin D3 (25-OH Cholecalciferol) Therapy on the Clinical Status in Adult Bahraini Patients with Systemic Lupus Erythematosus

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Abstract

The relationships between serum levels of Uric Acid (UA) and vitamin D3 (25-OH Cholecalciferol) in systemic lupus erythematosus (SLE) have been revealed separately; however, a possible link between these two factors and their interaction with SLE severity has not been clarified yet. This is the first study on investigating the conjoint association of vitamin D3 and UA on disease activity in Bahraini patients with SLE.

Objectives: To evaluate serum UA and serum vitamin D3 (VD) as important factors in clinical status in adult Bahraini patients with SLE and to look into the possible correlation between these two factors and their relation to disease activity in this patient's group.

Materials and methods: Fifty-one adult Bahraini SLE patients (mean age of 40.8 years, females were 84.3%) were included in this retrospective longitudinal (two-time points) study. Blood samples were taken before and after VD therapy 2-3 months apart at Salmanyia Medical Complex. All patients received oral VD therapy in form of tablets (50.000 IU) once per week for a maximum period of 3 months. Blood samples were obtained for determination of serum levels of VD, calcium, phosphorus, alkaline phosphatase (ALP) and parathyroid hormone (PTH), but also for serum UA, complements (C3 and C4), C-reactive protein (CRP), antinuclear antibodies (ANA) and anti-double-stranded (ds)- DNA antibody.

Results: The current study showed that VD therapy bring about two-fold increment in its mean serum level ($p<0.0001$) with increased in serum calcium ($p<0.05$). Wonderfully, the mean serum levels of ds-DNA auto-antibodies and UAUA were significantly decreased after VD therapy ($p=0.015$ and $p=0.010$, respectively). Interestingly, when the group was segregated by gender and age; the female group and the age group <40 years, independently, showed statistically significant difference in all parameters exactly as the whole group. Comparably, both the male group and the age group ≥ 40 years showed notable reduction in mean serum UA, but that was statistically not significant.

Conclusion: We evaluated serum UA and serum VD as important factors in SLE disease. Our study showed strong inverse correlation between these two factors, thus, the correction of hypovitaminosis in SLE patients resulted in reduced serum UA. The current study established that serum VD levels are inversely correlated with both serum uric acid and disease activity, undependably, in adult Bahraini patients with SLE. Consequently, we strongly recommend VD supplementation for Bahraini patients with SLE.

Keywords: Serum Vitamin D3 (Serum VD); Systemic Lupus Erythematosus (SLE); Serum Urea (Serum UA); Bahrain

Introduction

Vitamin D3 (25-OH Cholecalciferol) is a steroid hormone that has well-established roles in calcium regulation and bone metabolism [1-4]. Recently, vitamin D3 (VD) has become more recognized for its role in the immune response and its potential immunomodulatory effects in autoimmune diseases, including systemic lupus erythematosus (SLE). In SLE VD has been implicated in endothelial dysfunction [5]. On the other hand, its role in restoring immune homeostasis in SLE patients through its inhibitory effects on DC maturation and activation has also been reported [6]. VD deficiency was prevalent among South Asian, Middle Eastern and African women [7,8]. However, VD deficiency is more noticeable in patients with SLE in these regions [9,10].

Inadequate VD status can compound the problem of low BMD or osteoporosis, which is a known problem as steroid-induced in patient with SLE [11]. A longitudinal study in 2012 was highlighted the importance of prevention and treatment of VD deficiency and osteoporosis in SLE patients, especially those using glucocorticoids or antimalarials [12]. Moreover, association of VD insufficiency and flare in SLE has been established, however, if it is a predisposing factor for flare or a consequence of the flare itself in SLE patients has not been clarified [13]. Another study by Schoindre et al. has found a low VD status in the majority of patients with SLE with a modest association with high disease activity, but not between baseline level and relapse-free survival rate [14].

Coexistent of gout (high serum UA) and autoimmue rheumatic diseases such as SLE, progressive systemic sclerosis (PSS) and mixed connective tissue disease (MCTD) has been reported rarely. Unlike in rheumatoid arthritis where negative association with gout has been widely established, in SLE gout has been reported to be rare as only a few sporadic cases have been reported from 1985 to 2001 [15]. The rarely reported coexistent of gout and SLE could be due to the possibility that SLE prevents expression of gout, or vice-versa. Review of the reported cases suggests that SLE is likely to be inactive and serum complement

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normal when gout is active. Lack of awareness of the possibility of gout and concurrent treatment with corticosteroids and non-steroidal anti-inflammatory drugs may prevent recognition of gout in many patients with SLE [16]. In old study prevalence of high serum UA was found in 29% and was closely associated with renal involvement particularly proteinuria and diuretic therapy [17]. Gout should be considered in the differential diagnosis of patients with SLE who present with acute arthritis and/or subcutaneous nodules particularly in those with longstanding stable nephritis and receiving diuretics for concomitant hypertension [18]. Periarticular calcification seen in patients with SLE has been related to crystal induced arthritis that seemed to be associated with the use of diuretics in those patients [19].

After the year 2000 the concomitant gout and SLE have received increasing attention. High serum UA with SLE or PSS MCTD has rarely been reported, in MCTD a case report of intraarticular crystal deposition has been reported showing the importance of differentiating gout from the arthropathy in MCTD patients [15,20].

High UA in SLE patients is independently associated with the occurrence of hypertension, hyperlipidemia, arterial thrombosis, stroke, myocardial infarction, peripheral neuropathy [21], arterial stiffness and subclinical atherosclerosis without clinically evident atherosclerotic cardiovascular disease [22] and preterm birth [23]. High UA levels are also associated with pulmonary arterial hypertension (PAH) in SLE patients [24] and may be useful as a surrogate marker for screening of PAH in patients with SLE [25]. A recent study 2017 revealed that higher UA levels contribute to the development of new renal damage in SLE patients independent of other well-known risk factors for such occurrence [26].

Concomitant occurrence of gout and VD deficiency has been reported occasionally in SLE patients; however, the relation between these two factors is still debatable. Altered UA transport and VD metabolism in the proximal tubule was suggested as possible cause- and effect-relation between renal hypouricemia and high VD levels [27]. At the same time it has been reported that administration of allopurinol suppressed UA and increased VD levels in patients with chronic renal failure [28]. Earlier, study has suggested that serum UA may directly decrease serum VD in patients with gout by inhibiting 1alpha-hydroxylase activity [29].

Controversial correlations between serum VD and UA concentrations, as well as their interaction with disease activity has been reported in Parkinson disease [30]. In SLE patients, Grados et al. showed that in ambulatory elderly women with VD deficiency, supplementation with calcium plus VD appeared to be well tolerated with no significant effects on creatinine clearance, but on high serum UA [31]. In addition, a recent Chinese study revealed that insufficiency in serum VD was significantly associated with elevated UA in middle-aged and elderly women [32]. Other study demonstrated that allopurinol administration might be an effective drug to lower hyperuricemia, and to treat hypovitaminosis D [33].

The aim of the present study is to assess the association of elevated serum levels of UA and VD in Bahraini patient with SLE, but also, we aimed to investigate a possible link between these two factors, particularly their interaction with disease severity in Bahraini patients with SLE. We also intended to test the effects of VD therapy on its levels and on the disease activity in patients with SLE as assessed by ds-DNA antibodies and serum C3 and C4 levels.

Materials and Methods

A total of 51 adult (more than 12 years old) Bahraini patients with SLE were included in this retrospective longitudinal (two-time points) study, most of the patients were included in our previous study investigating VD status in adult Bahraini patients (total No 58) with SLE (In press, EIJI). Only 51 patients who received VD therapy were included in the current study. Blood samples were obtained for determination of VD serum levels and the factors which are involved in its regulation such as calcium, phosphorus, alkaline phosphatase (ALP) and parathyroid hormone (PTH). Determination of other factors such as serum UA, complement (C3 and C4), C-reactive protein (CRP) and some autoantibodies including, antinuclear antibodies (ANA), anti-double-stranded DNA (ds-DNA) were also performed. Measurement of the serum level VD was done using chemilumenescence immunoassay on Advia Centaur Analyzer (LoD 8.0 nmol/L). VD deficiency was considered as serum levels <30 nmol/L, levels between 30 nmol/L and 50 nmol/L (≥ 30 < 50) were considered as VD insufficiency and optimal levels were ≥ 50 nmol/L. The complements, C3 and C4, were done by automated nephlometry using seimens reagents and BN Prospect machine. ANA test was done by indirect immunofloresence (IIF) method using hep2 slides from BIORAD Company. Anti-dsDNA levels were tested by automated ELIA using uniCAP machine from Phadi (pharmacia diagnostics-Thermo scientific co). Calcium, phosphorus and alkaline phosphatase levels in the serum were analyzed using spectrosphometric technique on Advia Chemistry XPT Analyzer. Intact PTH was determined in serum by two-site sandwich immunoassay, using direct chemiluminometric technology on Advia centaur analyzer (analytical sensitivity 0.265 pmol/L).

Statistical Analysis

Data was entered and analyzed using SPSS version 23.0. Quantitative variables were presented as mean ± SD and qualitative variables were parented as counts and percentages. Paired t-test was used to test the significance difference in population means. P-value <0.05 was considered as statistically significant.

Results

Fifty-one Bahraini patients included in this study. The mean age of the patients was 40.8 years (range 13 – 61 years, SD=13.2). However, most of the patients are females 43 (84.3%).

Table 1, our results depicted in this table showed that VD serum level was significantly increased after VD therapy with an increment in the mean serum levels from 35.17 to 67.04 ($p<0.0001$). The serum calcium was also increased after VD therapy and there was statistical significant difference between the serum levels of calcium before and after the therapy ($p<0.05$). On the other hand, the mean serum levels of ds-DNA auto-antibodies and UA were significantly decreased after VD therapy from 207.41 to 49.56 (p=0.015) and from 349.84 to 301.69 (p=0.010), respectively.

Table 2 showed that when segregate the group by gender; the female group showed that there is statistically significant difference in serum VD (from 35.37 to 68.20, p=0.000), ds-DNA reduced from 195.56 to 30.67 (p=0.037), ALP reduce from 75.03 to 65.17 (p=0.020) and mean serum UA reduced from 345.07 to 287.78 (p=0.008). Regarding, the males group the difference was for VD from 33.07 to 60.00 (p=0.002), calcium increased from 2.10 to 2.27 (p=0.030), phosphorus reduced from 1.33 to 1.1 (p=0.018). UA did not change before and after therapy, mean serum levels were 375.60 and 376.80, respectively.

Table 3 showed segregation of patients according to the age irrespective to the gender, the age group<40 years showed increased

	Variables	Before		After		Mean diff.	95% C.I.		P-value
		Mean	SD	Mean	SD		Lower	Upper	
All	Vitamin D	35.17	12.72	67.04	21.26	-31.87	-38.11	-25.62	0.000
	Calcium	2.17	0.18	2.24	0.10	-0.07	-0.13	-0.01	0.025
	Phosphorus	1.36	0.62	1.21	0.21	0.15	-0.04	0.34	0.119
	PTH	6.55	4.29	6.26	4.56	0.29	-1.20	1.78	0.699
	ALP	72.30	25.38	66.86	21.02	5.43	-2.25	13.12	0.160
	C3	94.87	26.49	96.82	31.74	-1.95	-13.13	9.23	0.724
	C4	18.96	11.57	18.08	12.73	0.87	-1.92	3.67	0.529
	ds-DNA	207.41	394.98	49.56	111.74	157.84	32.89	282.79	0.015
	CRP	4.78	6.58	4.44	6.15	0.33	-1.28	1.95	0.674
	Uric Acid	349.84	105.87	301.69	106.92	48.16	12.30	84.01	0.010

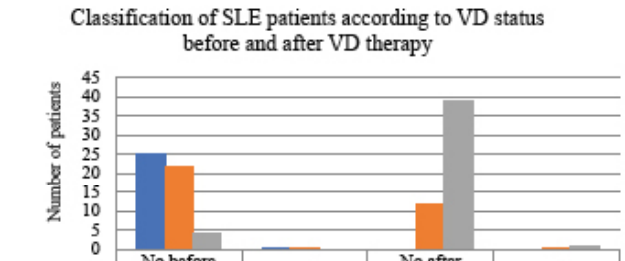
Table 1: Comparison of patient's lab results; before and after Vitamin D therapy.

	Variables	Before		After		Mean diff.	95% C.I.		P-Value
		Mean	SD	Mean	SD		Lower	Upper	
Female	Vitamin D	35.37	12.89	68.20	22.03	-32.83	-40.06	-25.60	0.000
	Calcium	2.18	0.18	2.23	0.10	-0.05	-0.12	0.02	0.139
	Phosphorus	1.37	0.66	1.23	0.22	0.14	-0.08	0.36	0.197
	PTH	6.50	4.05	5.78	3.62	0.71	-1.01	2.43	0.403
	ALP	75.03	26.40	65.17	19.82	9.87	1.66	18.07	0.020
	C3	96.80	24.96	99.44	31.38	-2.64	-13.05	7.76	0.606
	C4	18.70	12.19	18.00	13.30	0.70	-2.28	3.69	0.632
	ds-DNA	195.56	373.61	30.67	43.80	164.88	11.11	318.66	0.037
	CRP	5.57	7.27	4.39	6.90	1.18	-0.72	3.08	0.211
	Uric Acid	345.07	106.93	287.78	99.56	57.30	16.10	98.49	0.008
Male	Vitamin D	33.07	13.47	60.00	17.37	-26.93	-38.93	-14.94	0.002
	Calcium	2.10	0.11	2.27	0.11	-0.17	-0.31	-0.02	0.030
	Phosphorus	1.33	0.24	1.10	0.14	0.23	0.07	0.38	0.018
	PTH	6.82	6.09	9.00	7.78	-2.18	-5.76	1.39	0.177
	ALP	63.17	17.39	78.67	25.29	-15.50	-35.68	4.68	0.105
	C3	86.10	40.21	87.50	37.12	-1.40	-97.77	94.97	0.966
	C4	21.50	9.20	18.78	11.91	2.72	-10.82	16.26	0.607
	ds-DNA	286.25	523.94	129.08	233.19	157.17	-153.83	468.16	0.251
	CRP	1.66	1.44	4.82	2.75	-3.16	-5.10	-1.22	0.011
	Uric Acid	375.60	107.47	376.80	125.75	-1.20	-63.97	61.57	0.960

Table 2: Comparison of patient's lab results by sex before and after Vitamin D therapy.

	Variables	Before		After		Mean diff.	95% C.I.		P-value
		Mean	SD	Mean	SD		Lower	Upper	
< 40	Vitamin D	28.444	10.3766	65.61	20.10	-37.17	-47.25	-27.09	0.000
	Calcium	2.16	0.16	2.24	0.10	-0.09	-0.18	0.00	0.060
	Phosphorus	1.56	0.89	1.31	0.17	0.25	-0.20	0.70	0.249
	PTH	5.38	2.66	4.48	2.32	0.90	-1.28	3.08	0.387
	ALP	71.60	25.13	66.40	24.82	5.20	-8.47	18.87	0.428
	C3	93.25	24.19	87.45	28.24	5.80	-12.95	24.55	0.513
	C4	16.29	11.81	15.11	15.20	1.19	-4.02	6.39	0.630
	ds-DNA	302.78	471.65	101.48	165.73	201.31	-16.44	419.06	0.057
	CRP	2.20	2.65	3.25	3.56	-1.05	-4.02	1.91	0.447
	Uric Acid	369.92	107.87	312.77	106.42	57.15	20.38	93.92	0.005
≥ 40	Vitamin D	39.345	12.3762	67.92	22.26	-28.58	-36.78	-20.38	0.000
	Calcium	2.18	0.19	2.24	0.10	-0.06	-0.15	0.03	0.165
	Phosphorus	1.23	0.30	1.15	0.22	0.08	-0.06	0.22	0.261
	PTH	7.21	4.92	7.27	5.21	-0.06	-2.15	2.03	0.952
	ALP	72.77	26.13	67.18	18.61	5.59	-4.37	15.55	0.256
	C3	96.04	28.67	103.59	33.15	-7.54	-22.30	7.21	0.296
	C4	20.82	11.31	20.17	10.59	0.66	-2.83	4.14	0.699
	ds-DNA	143.82	333.90	14.96	18.84	128.87	-38.14	295.88	0.122
	CRP	6.55	7.89	5.26	7.44	1.29	-0.68	3.26	0.184
	Uric Acid	336.11	105.14	294.11	109.50	42.00	-15.98	99.98	0.145

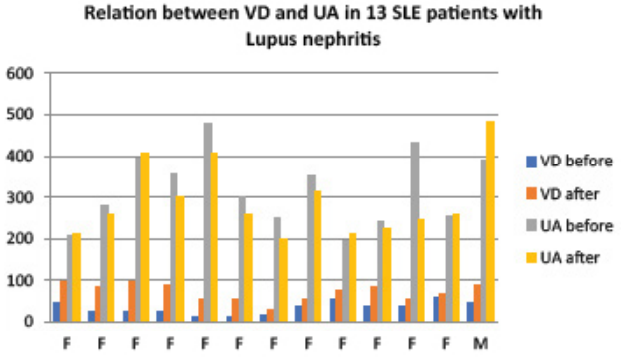
Table 3: Comparison of patient's lab results by age before and after Vitamin D therapy.



	No before therapy	%	No after therapy	%
Deficient	25	49%	0	0
Insufficient	22	43.10%	12	23.50%
Optimal	4	7.90%	39	76.50%

VD: Vitamin D, SLE: Systemic Lupus Erythematosus

Figure 1: Classification of SLE patients according to VD status before and after VD therapy.



VD: Vitamin D, UA: Uric Acid, SLE: Systemic Lupus Erythematosus, Before: Before Vitamin D Therapy, After: After Vitamin D Therapy, F: Female, M: Male

Figure 2: Relation between Vitamin D and uric acid in SLE patients with lupus nephritis.

mean serum levels of VD from 28.44 to 65.61 (p=0.000). UA reduced from 369.92 to 312.77 (p=0.005). For those >40 years old VD increased from 39.345 to 67.92 (p=0.000), while the mean serum UA reduced from 336.11 to 294.11, but that did not reach statistical difference.

Figure 1, showed the classification of VD status before and after VD therapy. Before the therapy the patients who were deficient 25(49%), Insufficient were 22 (43.1%) and optimal were 4 (7.9%). After VD therapy the patients who were deficient were zero (0%), insufficient were 12 (23.5%) and optimal were 39 (76.5%).

Figure 2, data depicted in this figure showed the relation between VD and UA in SLE patients with Lupus Nephritis. There were only 13 patients among our cohort with lupus nephritis 12 were female and only one male patients. In those patients mean serum level of VD was increased to two folds after therapy from 33.500 to 72.077 and the difference was statistically significant (p=0.0001). However, the mean serum UA was reduced from 318.31 to 293.54, but that was statistically not significant. Only in the male patient the UA level was increased significantly.

Discussion

The relationships between UA levels and serum VD with SLE have been revealed separately; however, a possible link between these factors and their interaction with SLE severity has not been exposed yet. This is the first study on investigating the conjoint association of VD and UA on disease activity in Bahraini patients with SLE.

We have previously described the VD status in Bahraini patients with SLE (In press, EIJI). We performed the present longitudinal study (at two time points) to expand the clinical data and to examine possible correlation between VD and UA by investigating the effect of correcting hypovitaminosis on serum UA, as well as, on clinical disease activity, as assessed by anti-ds-DNA and complements levels, in a well characterized group of patients. VD supplementation in patients with SLE was recommended previously since increased VD levels seemed to show tendency toward subsequent clinical improvement [34].

On classifying our current patients; according to their VD status as before and after VD therapy. We found that before the VD therapy there were 49% of the patients were deficient, 43.1% were insufficient and 7.9% were optimal. These results were consistent with our previous study in VD status (In press), that showed out of 53 SLE Bahraini patients 49.1% were deficient, 47.1% were insufficient, while only 2 (3.8%) patients were optimal. Stimulatingly, although only around 80% of our current patients are from patients included in our previous study, still we got same results. Only 20% were excluded of our previous patients, since we could not be able to find another time point or reading after VD therapy for those patients, thus, we included some new patients. Interestingly, in spite of the fact that these are not same patients or number our previous results are still reproducible. On the other hand, after VD therapy we found that none of our patients had VD deficiency, only 12 (23.5%) patients were insufficient and 39 (76.5%) patients achieved optimal (≥ 50 nmol/L) VD levels. The insufficient levels found in some of our patients could be due to either a second blood sample was taken before three months (maximum therapeutic period) or incompliance with the drug.

In the current study VD mean serum level was increased to two folds after VD therapy compared to the mean serum level before the therapy and the difference was statistically significant. The most interesting finding in our study was that with correction of the hypovitaminosis both UA and anti-ds-DNA antibodies serum levels were reduced significantly in our patients with normalization of VD serum levels. The mean serum level of complement (C3) were noted to be increased after therapy in all studied groups (Tables 1-3), but that did not reach statistical difference, however, there was no change in C4 before and after therapy.

The presentation of gout in SLE could be misinterpreted as SLE arthritis and might be modified or suppressed by VD therapy, since in our cohort both high serum levels of UA and high disease activity, as assessed by anti-ds-DNA antibodies levels, goes down with VD therapy. Our findings are consistent with other study which showed that serum VD levels are inversely correlated with SLE disease activity at both active and inactive disease status [35]. Another study revealed that hyperuricemia can suppress 1-α-hydroxylase and lead to decreasing VD concentration [30]. One more study has suggested that UA per se may directly decrease serum VD since administration of anti-gout therapy to patients with gout was associated with a significant decrease in serum UA, but a significant increase in serum VD, admitting that serum concentrations of VD was not affected by those drugs [33]. Our results of decreased ds-DNA autoantibodies together with increased levels of C3 could indicate decreased disease activity and may result in clinical improvement. These results together with reduced serum UA should be confirmed with another prospective study assessing the patients clinically.

The mean age of our patients is 40 years. Therefore, we classified the patients into two groups less than 40 years and forty or more. Interestingly, when we segregated the patients according to the age irrespective to the gender we found that in the patient's group less than 40 years, VD therapy accompanied by statistical significant reduction in serum UA. However, in age group 40 years or more, the mean serum UA reduced, but that did not reach statistical difference.

When we segregated the group by gender; the female group showed statistically significant difference, thus, with increased serum VD levels there was a statistically significant reduction in ds-DNA, ALP and serum UA. However, the notable reduction of Pho, PTH or CRP did not reach statistical significance. Regarding, the males group the increased VD levels after therapy accompanied by statistically significant increase in serum calcium and reduction in phosphorus. Moreover, the notable reduction in ds-DNA, C4 and UA along with the notable increase in C3 did not reach statistical significance. On the contrary, only in this male group the mean serum UA did not change, moreover, the mean serum level of CRP was increased and that was statistically significant. CRP is an acute phase protein that is known as biomarker, its level traditionally used to detect or predict outcome of infection, inflammation or monitor efficacy of therapy. In the current study the rationale behind low CRP in our SLE patient's cohort before the therapy and the more reduction in mean serum levels after therapy in all studied groups except the male group was not fully understood. However, the possible role of CRP in the handling and clearance of immune complexes in patients with SLE has been suggested [36]. The association of VD deficiency and CRP was occasionally reported. One study reported an association between hypovitaminoses D and inflammatory markers (hsCRP) that contributed to CVD and that VD may be important in maintaining cardiovascular health [37]. Another study revealed that VD was not associated with any measure of subclinical atherosclerosis, but VD deficiency was associated with higher hsCRP at baseline, but then again did not predict a change in hsCRP over time [22,38].

In an ambulatory elderly women with VD deficiency, supplementation with calcium and VD appeared to be well tolerated without effects on creatinine clearance, but with elevated serum UA concentrations [39]. SLE patients, especially those with leucopenia or renal involvement, are at high risk of VD deficiency and require VD supplementation [22]. On the other hand, the UA level has been shown to be independently associated with the development of LN in SLE patients [35]. Recent study, in Bahraini SLE patients performed by our group, revealed that the presence of anti-Smith, anti-Ro/SSA and anti-RNP antibodies and the absence of anti-dsDNA antibodies are independent predictive markers for renal involvement. However, VD levels was not investigated at time [40-42]. In our current study (Figure 2), there was only 13/51 SLE patients with biopsy proven lupus nephritis (LN). All were females except one male patient. Our results showed that the two folds increment in VD serum level, which was statistically significant, accompanied by notable reduction in serum UA, but that did not reach statistical significant. On the contrary, significant increase in serum UA was noticed for our male patient. Due to small number of patients with LN we could not be able to draw any conclusion as high UA or Low VD could be consider as risk factors for development of LN in Bahraini patient with SLE.

Conclusion

We evaluated serum UA and serum VD as important factors in SLE disease. Our study showed strong inverse correlation between these two factors, thus, the correction of hypovitaminosis in SLE patients may result in clinical improvement. The current study established that serum VD levels are inversely correlated with both serum UA and disease activity, undependably, in adult Bahraini patients with SLE. We recommend VD supplementation for patients with SLE as this may induce clinical improvement and prompt disease inactivity.

Limitation of Our Study

The present study has some potential limitations; being a retrospective study is one factor. In addition to, VD levels are variables and were measured at only two time points (longitudinal) during the study, but the second sample in some samples was not taken at the end of the therapeutic period, which should be minimum three months for the oral therapy. Also, our sample was small in this longitudinal retrospective study; hence our findings should be interpreted cautiously. Unavailability of data on dietary intake of VD containing foods, as well as, important factors such as; medications, body mass index (BMI) and genetics can be considered as another important limitation.

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