

Vitamin D Deficiency in Patients with Systemic Lupus Erythematosus in Suez Canal University Hospital

Nada A. Motawei¹, Gamal A. Tawfik¹, Hanan H. Omar², and Ayman Salem^{1*}

¹Internal Medicine Department, Suez Canal University Hospitals, Faculty of Medicine, Suez Canal University, Ismailia, Egypt. ²Clinical Pathology Department, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.

Abstract

Background: Systemic Lupus Erythematosus (SLE) is a multi-system chronic inflammatory autoimmune disease that compromises multiple organs and unpredictable course and prognosis. Vitamin D deficiency is implicated as a potential environmental factor triggering some autoimmune disorders, including SLE. **Aim:** To improve the management of SLE patients and reduce disabilities arising as a consequence of vitamin D deficiency. **Objectives:** Our objectives were to assess the prevalence of vitamin D deficiency in SLE patients and its relation to disease activity and renal involvement in those patients. **Patients and Methods:** We enrolled 72 SLE patients who fulfilled the revised classification criteria of the American College of Rheumatology whose ages were above or equal to 16 from both genders and who visited the outpatient clinic or were admitted to the inpatient departments of the Suez Canal university hospital. They were subjected to full medical history, examination, SLE disease activity index –SLEDAI- score assessment, and lab investigations (CBC, C3, C4, ESR, urine analysis, 24-hour urine protein, and vitamin D. **Results:** The mean of vitamin D level was nearly 19ng/ml ranging from 5 to 38ng/ml and 55.6% of the patients showed deficient level (< 20ng/ml). Our variables (disease activity, renal involvement, age, gender, BMI, and laboratory findings) were not correlated to vitamin D level except for disease duration which showed a strong negative relationship where vitamin D deficiency is remarkable when SLE duration exceeds 6 years (100%) " $R = -0.797$ and $P > 0.001$ ". **Conclusion:** vitamin D deficiency is a common problem in SLE patients, also vitamin D deficiency was related to disease duration but not to disease activity or renal involvement.

Keywords: Hypovitaminosis D, autoimmune disorders, proteinuria, Systemic Lupus Erythematosus, vitamin D

Introduction

Systemic Lupus Erythematosus (SLE) is a multi-system chronic inflammatory autoimmune disease that may compromise multiple organs also of unpredictable course and prognosis. Primarily it affects young women of reproductive age, at a

ratio of nine women for every man with prevalence ranging from 20 to 150 cases/100,000 individuals^(1,2). Also, the etiology of SLE is still obscure and its progression apparently involves the interaction of genetic, hormonal, environmental, and immune factors⁽²⁾. Several studies have shown that ethnicity plays a vital role in determining the clinical features and disease

*Corresponding Author: aymansalem2010@yahoo.com

outcome in patients with SLE⁽³⁾. Vitamin D deficiency has been implicated as a potential environmental factor triggering some autoimmune disorders, including SLE, since several immune-regulatory activities for 1, 25(OH)₂D₃ have been identified⁽⁴⁾. In addition, it has been suggested that patients with SLE; especially those with increased disease activity have decreased vitamin D levels, indicating that vitamin D might play a role in regulating autoantibody production⁽⁵⁾. Vitamin D is the common denominator of a group of sterols with a crucial role in phospho-calcic metabolism. The main source of vitamin D is the conversion of 7-dehydrocholesterol to pre-vitamin D₃ in the skin, by means of solar ultraviolet B radiation and a lesser amount of vitamin D is obtained from food. Vitamin D₃ undergoes a 25-hydroxylation in the liver, with the resulting product, 25(OH) D or calcidiol, being the main circulating form of vitamin D. 25(OH) D levels are therefore used to determine the vitamin D status of a given individual⁽⁶⁾. Also, Vitamin D insufficiency was detected in a lot of patients and might also play a role in bone metabolism disturbance. Reduced calcitriol levels are thought to impair bone mineralization by limiting the amount of available calcium and phosphorus and favor bone resorption by stimulating PTH synthesis and secretion. Moreover, some studies suggest that 25-hydroxyvitamin D levels might also influence osteoblast proliferation and functions (through autocrine pathways)^(7,8). Also, some studies indicate that renal involvement is also related to a higher risk for vitamin D deficiency in SLE patients⁽⁹⁾. Others conclude that SLE patients with LN have significantly lower vitamin D levels than inactive SLE and active SLE without LN. Hence, Nephritis is a significant predictor of vitamin D deficiency in SLE patients⁽⁹⁾. SLE patients, especially those with

leucopenia or renal involvement are at high risk of vitamin D deficiency and require vitamin D supplementation. Some SLE patient sera contained 1, 25(OH)₂D₃ antibodies but these antibodies do not appear to affect vitamin D levels⁽¹⁰⁾. Several studies have been done regarding this issue internationally. In a study conducted in the Brazilian northeastern state of Pernambuco, in which vitamin D insufficiency was seen in 57.7% of 78 patients with SLE. Three other Brazilian studies support these findings⁽¹¹⁾. Also, Vitamin D inadequacy is highly prevalent in Saudi patients with SLE⁽¹²⁾ and in Egyptian SLE patients despite plentiful exposure to sunlight throughout the year, and its level is negatively correlated to disease activity as mentioned in Ain shams study in 2011⁽¹³⁾. And as a result of the previously mentioned data and as no studies have looked into SLE patients in our university we aimed to assess the prevalence of vitamin D insufficiency and deficiency in our patients with lupus to help patients for better prognosis and to see the importance of adding vitamin – D supplementation to their management.

Patients and Methods

This is a cross-sectional study that recruited 72 SLE patients who visited the outpatient clinic (of nephrology and/or rheumatology department) and who were admitted to the inpatient (of nephrology and/or rheumatology department) of Suez Canal university hospital. SLE patients who fulfilled the revised classification criteria of the American College of Rheumatology for SLE patients whose ages were above or equal to 16 and of both genders were included. Patients who refused to participate, or were on regular supplementation with vitamin D, or had chronic liver disease, chronic kidney disease, or ESRD were excluded from the study.

Methods

All patients fulfill inclusion criteria were subjected to Full medical history, clinical examination, Systemic Lupus Erythematosus disease activity score (SLEDAI) assessment, and laboratory testing for CBC, C3, C4, ESR, urine analysis, 24-hour urine protein, and vitamin D.

Assessment of vitamin D

Total 25-OH Vitamin D EIA Kit was used (Enzyme Immunoassay for the quantitative measurement of total 25-OH Vitamin D_{2/3} levels in serum or plasma). No special preparation of individuals was necessary prior to specimen collection. Whole blood was collected with Vacutainer and serum was separated from the cells according to the manufacturer's instruction then samples were kept at -15°C. Test samples were added directly to wells of a microtiter plate that was coated with specific anti- OH Vitamin D₂, D₃ antibodies. A buffer designed to release Vitamin D from binding proteins was then added to the wells. After the first incubation period, unbound material was washed away, and biotinylated Vitamin D analog was added to the wells and binds to the remaining antibody sites. After the second incubation period, unbound biotin-D was washed away, and horseradish peroxidase (HRP) conjugated streptavidin was added to each well. During the third incubation step, an immune complex of well coated "vitamin D antibody – vitamin D, biotin D and HRP conjugated streptavidin" was formed. The unbound matrix was removed in the subsequent washing steps. For the detection of this immunocomplex, the well was then incubated with a substrate solution in a timed reaction, which was terminated with an acidic reagent (ELISA stop solution). The absorbance was then measured in a spectrophotometric

microplate reader. The enzymatic activity of the immunocomplex bounded to the wall of each microtiter well was inversely proportional to the amount of total 25-OH D_{2/3} in the test sample. A calibration curve was generated by plotting the absorbance versus the respective Vitamin D concentration for each calibrator on a 4- parameter or point-to-point curve fitting. The concentration of a total of 25-OH Vitamin D_{2/3} in test samples was determined directly from this calibration curve.

Results

Only four cases of the study population were males. The mean age was nearly 33 years old ranging from 17 to 52 years. There were 21(29.17%) has normal weight, 22 (30.56%) overweight, and 29 (40.27%) obese patients. The mean disease duration was nearly 6 ranging from 1 to 9 years (Table 1). There were 36 (50%) of the whole population with no activity while the other half of the population who has activity, the highest percent was for those who have very high activity (31.9%). The mean SLEADI score was nearly 12 ranging from 0 to 34 (Table 2). Table (3) shows that the mean hemoglobin level was nearly 11 g/dl ranging from 7 to 15 g/dl, mean total leukocyte count was nearly 6000 /μl ranging from 2300 to 10500 /μl, and mean platelets count was nearly 232 x10³/μl ranging from 65 to 450 x10³/μl. Table (4) shows that mean c3 was nearly 80 mg/dl ranging from 15 to 160 mg/dl. Mean c4 was nearly 21mg/dl ranging from 3 to 40 mg/dl. ESR highest level goes for those who have ESR < 20 with 43.1% while individuals who have ESR >100 were 18 showing the lowest percent (25%).

Table 1: Demographic and descriptive data of the studied population		
Variables		Patients (N = 72)
Gender	Male	4 (5.6%)
	Female	68 (94.4%)
Age (Year)	Mean $\pm$ SD	32.99 $\pm$ 9.187
	Range	17-52
BMI	Normal	21 (29.17%)
	Overweight	22 (30.56%)
	Obese	29 (40.27%)
SLE Duration (yrs.)	Mean $\pm$ SD	6.15 $\pm$ 1.67
	Range	1-9

Table 2: Degree of activity among the studied population (n=72)	
Degree of activity (SLEDAI score)	
Mean $\pm$ SD	12.32 $\pm$ 13.39
Range	0-34
No activity: 0 (no. %)	36 (50%)
Mild: 1-5 (no. %)	0
Moderate: 6-10 (no. %)	3 (4.2%)
High: 11-19 (no. %)	10 (13.9%)
Very high: $\geq$ 20 (no. %)	23 (31.9%)

Table (5) shows that half of the population has a normal picture for the urine analysis while the other half shows 30 (41.7%) out of 36 have proteinuria and 6 (8.3%) has both hematuria and proteinuria. Out of those who have proteinuria the highest percent-

age goes for those who have protein +1 (25%) and the lowest for those who have protein +2 (9.7%) while the heavy proteinuria - protein +3- appears in 11 (15.35) of them. The mean 24-hour urine protein collection was nearly 1 ranging from 0 to 5.

Table 3: Hematological findings among the studied population		
Variables	Mean $\pm$ SD	Range
HB (g/dl)	11.2 $\pm$ 2.35	7:15
TLC ($n \times 10^3$ /ul)	6.4 $\pm$ 2.4	2.3:10.5
Platelets ($n \times 10^3$ /ul)	232.7 $\pm$ 101.7	65-450

Table (6) shows the mean of vitamin D was nearly 19 ng/ml ranging from 5 to 38 ng/ml. More than half of the population shows a deficient level of 40 (55.6%) while only 4 (5.6%) show a sufficient level. Table (7) shows that our variables were not correlated

except for the disease duration as ($R = -0.797$ and $P > 0.001$) "A strong downhill (negative) linear relationship". Table (8) shows that deficiency of vitamin D is remarkable when the SLE duration exceeds 6 years (100%) while when disease duration is ≤ 6 years

there is no deficiency, but vitamin D level shows insufficiency (87.5%) and only small percent (12.5%) shows sufficient level. The mean level of vitamin D is higher in the disease duration ≤ 6

years than duration >6 years. According to disease duration, there were statistically significant differences concerning the vitamin D level or the degree of deficiency.

Table 4: Immune markers of the studied population		
Variables		Patients (N = 72)
C3 (mg/dl)	Mean $\pm$ SD	80.25 $\pm$ 43.02
	Range	15:160
C4 (mg/dl)	Mean $\pm$ SD	20.9 $\pm$ 11.37
	Range	3-40
ESR (ml/hr.)	<20	31 (43.1%)
	20:100	21 (31.9%)
	>100	18 (25%)

Table 5: Urine findings among the studied population		
Variables		Patients (N = 72)
Urine analysis	Normal	36 (50%)
	Proteinuria	30 (41.7%)
	Isolated Hematuria	0
	Mixed	6 (8.3%)
Proteinuria degree	No	36 (50%)
	+1	18 (25%)
	+2	7 (9.7%)
	+3	11 (15.3%)
24 hr. urine protein (gm/day)	Mean $\pm$ SD	1.04 $\pm$ 1.66
	Range	0-5

Discussion

Our results are comparable to the findings reported by Abaza et al. a study on Egyptian SLE patients in which the overall prevalence of suboptimal and deficient vitamin D is 96%⁽¹⁴⁾. Also to study by Ruiz-Irastorza et al. reported that 90% had suboptimal and deficient vitamin D levels despite the fact that their population resides in a south European country with plenty of sunny days⁽¹⁵⁾. The difference between both our results, Abaza et al. results, and that of Ruiz-Irastorza et al. might be due to

vitamin D supplementation in some patients in the previous study while none in the current study received any at the time of entry. Similarly, in a study on the Chinese patients with SLE in which the prevalence of vitamin D deficiency was 91.7% and the difference in the prevalence from 94.5% in our study and their prevalence might be due to the smaller number of our population which is 72 while their own was 121⁽¹⁶⁾. In contrast, Abou-Raya et al. conducted a study on Egyptian SLE patients and found that the overall prevalence of suboptimal and deficient 25(OH)D

serum levels among patients with SLE was 69%⁽¹⁷⁾ and Salman-Monte et al. conducted a study on Mediterranean

region in which the overall prevalence of insufficient and deficient vitamin D were 46%⁽¹⁸⁾.

Table 6: Vitamin D level among the studied population	
Vitamin D (ng/ml)	Patients (N = 72)
Mean $\pm$ SD	18.5 $\pm$ 5.9
Range	5-38
Sufficient: 30-100	4(5.6%)
Insufficient: 20-29	28 (38.9%)
Deficient: <20	40 (55.6%)

Table 7: Correlations between vitamin D and other variables							
Demographic and clinical Variables	Activity	Renal	Age	Gender	Duration	BMI	SLEADI Score
Vitamin D Level							
Pearson Correlation	.012	.009	.109	-.041	-.797**	.081	.032
Sig. (2-tailed)	.922	.937	.360	.735	.000	.499	.790
Laboratory Variables	HB	TLC	Platelet	C3	C4	ESR	24-hr protein
Vitamin D Level							
Pearson Correlation	-.016	.114	-.021	-.019	-.015	-.204	-.139
Sig. (2-tailed)	.892	.341	.863	.874	.900	.085	.245

This is because patients in both studies were on vitamin D supplementation while in our study there were none of our patients on supplementation. Similarly, Kamen et al. found vitamin D insufficiency and critical deficiency in nearly 85% (67% and 17.8% respectively) of the SLE patients in their study⁽³⁾. These results are within a cohort of newly diagnosed SLE patients and that's why it might be not similar to our study as the population in our study wasn't newly diagnosed. Our results showed no significant correlation between vitamin D insufficiency and deficiency and

different age groups. These results are comparable to the findings reported by Abaza et al. where $P = 0.17$ and the mean age was 29.6 ± 10 ranging from 16-59 years⁽¹⁴⁾, Amital et al. where $P = 0.15$, $R = 0.07$, and the mean age was 40 ± 14.2 ranging from 13-77 years⁽¹⁹⁾, the study on the Mexican patients where $P = 0.4$ and the mean age was 45.5 ± 12.6 ⁽²⁰⁾, the study on Mediterranean region where $P = 0.5$ and the mean age 52.4 ± 15.7 ranging from 39-66 years⁽¹⁸⁾ and the study on Chinese patients where $P = 0.9$ and the mean age was 52.4 ± 15.7 ranging from 0.5-236 month⁽¹⁶⁾.

Table 8: Relation between vitamin D and disease duration				
		Duration ≤ 6 years (N = 32)	Duration > 6 years (N=40)	P value
Vitamin D (ng/ml)	Sufficient	4 (12.5%)	0	0.001
	Insufficient	28 (87.5%)	0	
	Deficient	0	40 (100%)	
	Mean $\pm$ SD	23.67 $\pm$ 4.53	14.39 $\pm$ 2.95	0.001
	Range	20-38	5-19	

In contrast; Kamen et al. showed that There was a trend toward lower levels with increasing age in⁽³⁾. All the previous studies didn't examine the relation between disease activity, renal involvement, and age except the last one on the Chinese people which showed that there was no relation between disease activity and age as resulted in our study ($P= 0.4$ and 0.3 respectively). Differences in study design; characteristics of study groups and reference values of 25(OH) D make a direct comparison between studies very difficult. Regarding gender distribution; our results are comparable to results by Amital et al. (that included 347 females and 31 males) where the mean of Vit D for females was 20.5 ± 14.4 ng/ml and for males was 21.7 ± 13.2 ng/ml, $p= 0.6$ ⁽¹⁹⁾,

the study on the Saudi patients where $P= 1$, female to male ratio was 8.7:1, the mean for females was 19 ± 9.3 ng/ml and for males was 19.5 ± 11.6 ng/ml⁽¹²⁾, the study in Serbia where $P= 0.964$ and $R=0.002$ ⁽²¹⁾ and the study on Chinese patients where $P= 0.9$ and the mean age was 52.4 ± 15.7 ranging from 0.5-236 month⁽¹⁶⁾. In contrast, Ruiz-Irastorza et al. showed that females had higher levels of vitamin D ($P= 0.001$), this difference may be due to the smaller number of our population ($n=72$) than their population ($n=92$) and also because the females number in our study (86.7%) was lesser than the females' number in their study (90%)⁽¹⁵⁾. Also, there were no significant relations between disease activity, renal involvement, and gender ($P= 0.2$ and 1 respectively).

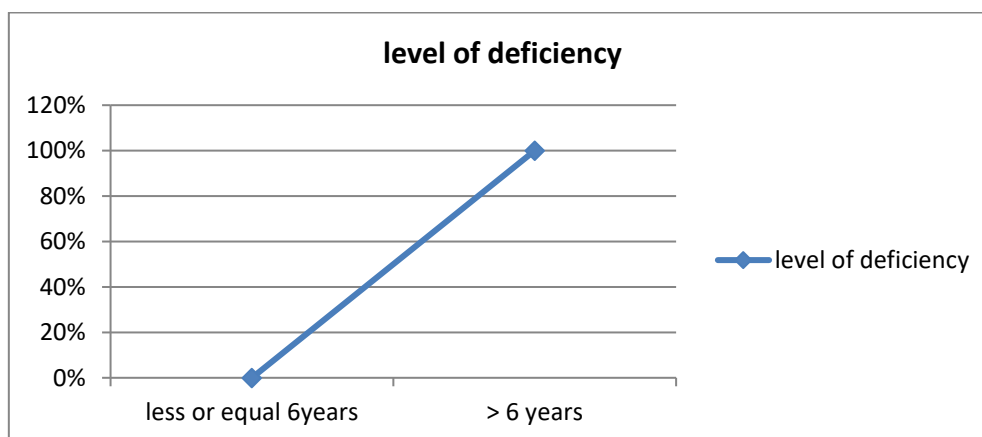


Figure 7: correlation between vitamin D deficiency and disease duration among SLE patients.

Regarding BMI; our results are comparable to the findings reported by Abou-Raya et al. where $P= 0.19$ ⁽¹⁷⁾, the study on Chinese patients where $P= 0.4$ ⁽²²⁾, and the study on the Mexicans where $P= 0.2$ ⁽²⁰⁾. In contrast, other studies showed a significant correlation between vitamin D deficiency and higher BMI, in which when BMI is higher the level of deficiency would be greater

like that study on Chinese people where $P= 0.03$ ⁽¹⁶⁾, study on Mediterranean region where $P=0.04$ and mean of vitamin D was 25.5 ± 4.7 ng/ml⁽²³⁾ and wright et al. a cohort study in pediatrics with SLE where $P= 0.004$ ⁽²⁴⁾. The study on the Chinese people showed that there was no significant relationship between disease activity and BMI where $P=0.9$ and which is nearly similar to

what is found in our study where $P = 0.399$. Also, our study shows no significant relation between renal involvement and BMI $P = 0.575$. In this study there was a significant correlation between vitamin D insufficiency and deficiency and disease duration as mentioned before, In contrast; findings reported by Abaza et al. where $R = 0.174$, $P > 0.005$ and the mean disease duration was 4.4 ± 0.6 ranging from 1-14 years⁽¹⁴⁾, Amital et al. where $P = 0.31$, $R = 0.05$ and the mean duration was 9.7 ± 7.5 years⁽¹⁹⁾, the study on the Mexican patients where $P = 0.23$ and the mean duration was 10.3 ± 6.7 ⁽²⁰⁾, the study on Mediterranean region where $P = 0.3$ and the duration ranging from 1-7 years⁽²³⁾, Abou-Raya et al. where $P = 0.17$ and the mean duration was 8.3 ± 6.9 ⁽¹⁷⁾ and studies which were reported by Ruiz-Irastorza et al., in Serbia by Miskovic et al. and Toloza et al.⁽²⁵⁾. Our study population wasn't on vitamin D supplementation versus some of the other previously mentioned studies. Also, the seasonal variations, the difference in the study design, reference values of 25 (OH) D from one study to another one, and the different ethnicities may explain the variations between our study and the other ones. Our study shows no significant relationship between disease duration and disease activity or renal involvement ($P = 0.136$, 0.953 respectively). Speaking about disease activity; our results are comparable to the findings reported by Ruiz-Irastorza et al. where $P = 0.46$ showing no difference in SLEADI score when patients had critically low vitamin D level or not⁽¹⁵⁾, the study on the Mexican patients where The levels of 25(OH)D were slightly lower in the group of patients with activity, compared to those with no activity; however, this difference was not statistically significant (19.3 ± 4.5 ng/mL versus 19.7 ± 6.8 ng/mL, $P = .75$) and the 25(OH)D levels were not related to the MEX-SLEDAI values $P = 0.21$ ⁽²⁰⁾, the study on Mediterranean

region where $P = 0.9$ showing no difference in SLEADI score when patients had low vitamin D level⁽¹⁸⁾, the cohort study about the Prevalence and predictors of vitamin D deficiency in non-supplemented women with SLE in the Mediterranean region where there was no significant relation between SLEADI score and vitamin D deficiency $P = 0.31$, Toloza et al. and the study on Brazilian patients by Souto et al.^(25,26). In contrast; findings reported by Abaza et al. where $R = -0.495$, $P < 0.001$ there was a high significant negative correlation between vitamin D deficiency and disease activity⁽¹⁴⁾, Abou-Raya et al. where there was an inverse correlation between deficiency and SLEADI score $P = 0.05$ ⁽¹⁷⁾, Amital et al. pooled several cohorts on Israel and Europe where there was weak but significant correlation; mean of vitamin D deficiency 17.8 ± 12.8 , $R = -0.12$ and $P < 0.0001$ ⁽¹⁹⁾, Yeap et al. where $P = 0.033$ ⁽²⁷⁾ and Borba et al. where $P = 0.0005$ ⁽²⁸⁾. This difference may be explained in our study by the small sample size and the small number of patients who show activity to demonstrate the effect of vitamin D deficiency on them, also vitamin D deficiency may reflect the tendency of patients that are ill with active lupus to avoid sunlight. Some of the other studies were similar to our results; activity was limited to those who had mild and moderate forms and the population with these two forms of activity might be not ideal to demonstrate the effect of deficiency on activity. At the time Our results showed no significant correlation between vitamin D insufficiency and deficiency and renal involvement, this may be because half of the patients with renal involvement have proteinuria +1 and it may need a larger number of patients with heavy proteinuria to be able to do this comparison, also this may occur as a result of that all of our patients don't have impaired kidney function which is a serious confounder as hydroxylation

will be affected and this will lead to deficiency. These results are comparable to the findings reported by Abaza et al. where $P=0.33^{(14)}$, study in Serbia which showed no association between vitamin D deficiency and lupus nephritis ($P=0.171, R=1.87^{(21)}$) and findings reported by Ruiz-Irastorza et al.⁽¹⁵⁾. While on the other hand, Kamen et al. showed that there was a significant relation between vitamin D deficiency and renal disease ($P=0.01^{(3)}$) and this can be explained by the presence of patients with renal impairment in this study. Also, our study showed that there is a statistically significant relation between renal involvement- in the form of the degree of proteinuria ($P=0.09$) and 24-hour urine protein with a mean 1.79 ± 1.96 gm/day ranging from 0-5 with ($P=0.01$) and disease activity. This is comparable to the study on Chinese patients where significant relation between activity scores and vitamin D level was confined to active renal disease. Regarding different lab findings; our results are comparable to the findings reported by the study on Mediterranean region where P value for C3, C4 and ESR was 0.79, 0.389, 0.881 respectively⁽¹⁸⁾. In contrast; findings reported by Abaza et al. where $R=0.323$, $P=0.012$ for ESR and $R=0.324$, $P=0.011$ for C4⁽¹⁴⁾, Abou-Raya et al. where there was a significant decrease in levels of disease activity markers in vitamin D group compared to placebo $P<0.005$ and marked decrease in the ESR level and increase in C4 level post 12 months of supplementation with vitamin D⁽¹⁷⁾. This difference may be explained in our study by the small sample size and the small number of patients who show activity to demonstrate the effect of vitamin D deficiency on them.

Conclusion

Vitamin D deficiency is a common problem in SLE patients, also vitamin D deficiency

incidence increases with increased disease duration with no association with disease activity or renal involvement. Further studies are needed to understand the role of vitamin D deficiency in the pathogenesis and clinical consequences of SLE.

References

1. Carvalho M, Bértolo M, Pinto M. (2008). Artrite Reumatoide In: Carvalho MAP, Lanna CCD, Bertolo MB. Reumatologia Diagnostico e Tratamento: Rio de Janeiro: Guanabara-Koogan. 309-328.
2. Grammatikos AP, and Tsokos GC. (2012). Immunodeficiency and autoimmunity: lessons from systemic lupus erythematosus. Trends in molecular Med. 18(2), 101-108.
3. Kamen D, and Aranow C. (2008). Vitamin D in systemic lupus erythematosus. Curr opin Rheumatol, 20(5), 532-537
4. Adorini L, and Penna G. (2008). Control of autoimmune diseases by the vitamin D endocrine system. Nat Clin Pract Rheumatol, 4(8), 404.
5. Cutolo M, Pizzorni C, Sulli A. (2011). Vitamin D endocrine system involvement in autoimmune rheumatic diseases. Autoimmun Rev, 11(2), 84-87.
6. Sypniewska G, Sobanska I, Pater A, et al. (2010). Does serum osteoprotegerin level relate to fragility fracture in elderly women with low vitamin D status? Med Sci Monit, 16(2), CR96-CR101.
7. Dias C, Dos Reis L, Caparbo V, et al. (2007). Decreased in vitro osteoblast proliferation and low turnover bone disease in nonuremic proteinuric patients. Kidney Int, 71(6), 562-568
8. Zhou S, LeBoff MS, Waikar SS, et al. (2013). Vitamin D metabolism and action in human marrow stromal cells: effects of chronic kidney disease. J Steroid Biochem Mol Biol, 136, 342-344.
9. Sumethkul K, Boonyaratavej S, Kitumnuaypong T, et al. (2013). The predictive factors of low serum 25-

- hydroxyvitamin D and vitamin D deficiency in patients with systemic lupus erythematosus. *Rheumatol Internat.* 33(6), 1461-1467.
10. Bogaczewicz J, Sysa-Jedrzejowska A, Arkuszewska C, et al. (2012). Vitamin D status in systemic lupus erythematosus patients and its association with selected clinical and laboratory parameters. *Lupus*, 21(5), 477-484.
 11. Monticeli O, Brenol J, Chies J, et al. (2012). The role of Bsm I and Fok I vitamin D receptor gene polymorphisms and serum 25-hydroxyvitamin D in Brazilian patients with systemic lupus erythematosus. *Lupus*, 21(1), 43-52.
 12. Damanhour L. (2009). Vitamin D deficiency in Saudi patients with systemic lupus erythematosus. *Saudi Med J*, 30(10), 1291-1295.
 13. Hamza RT, Awwad KS, Ali MK, et al. (2011). Reduced serum concentrations of 25-hydroxy vitamin D in Egyptian patients with systemic lupus erythematosus: relation to disease activity. *Med Sci Monit*, 17(12), CR711.
 14. Abaza NM, El-Mallah RM, Shaaban A, et al. (2016). Vitamin D deficiency in Egyptian systemic lupus erythematosus patients: how prevalent and does it impact disease activity? *Integr Med Insights*, 11, 27.
 15. Ruiz-Irastorza G, Egurbide M, Olivares N, et al. (2008). Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. *Rheumatology*, 47(6), 920-923.
 16. Gao C, Liu S, Wu Z, et al. (2016). Severe vitamin D deficiency increases the risk for moderate to severe disease activity in Chinese patients with SLE. *Lupus*, 25(11), 1224-1229.
 17. Abou-Raya A, Abou-Raya S, Helmii M. (2013). The effect of vitamin D supplementation on inflammatory and hemostatic markers and disease activity in patients with systemic lupus erythematosus: a randomized placebo-controlled trial. *J Rheumatol*, 40(3), 265-272.
 18. Salman-Monte TC, Torrente-Segarra V, Almirall M, et al. (2016). Prevalence and predictors of vitamin D insufficiency in supplemented and non-supplemented women with systemic lupus erythematosus in the Mediterranean region. *Rheumatol Internat.* 36(7), 975-985.
 19. Amital H, Szekanecz Z, Szűcs G, et al. (2010). Serum concentrations of 25-OH vitamin D in patients with systemic lupus erythematosus (SLE) are inversely related to disease activity: is it time to routinely supplement patients with SLE with vitamin D? *Ann Rheu Dis.* 69(6), 1155-1157.
 20. García-Carrasco M, Mendoza-Pinto C, Etchegaray-Morales I, et al. (2017). Vitamin D Insufficiency and deficiency in Mexican patients with systemic lupus erythematosus: prevalence and relationship with disease activity. *Reumatología Clínica (English Edition)*, 13(2), 97-101.
 21. Miskovic R, Plavsic A, Raskovic S, et al. (2015). Vitamin D status in patients with systemic lupus erythematosus in Serbia: correlation with disease activity and clinical manifestations. *Macedonian J Med Sci.* 3(2), 256.
 22. Mok CC, Birmingham DJ, Leung HW, et al. (2011). Vitamin D levels in Chinese patients with systemic lupus erythematosus: relationship with disease activity, vascular risk factors and atherosclerosis. *Rheumatology*, 51(4), 644-652.
 23. Muñoz-Ortego J, Torrente-Segarra V, Prieto-Alhambra D, et al. (2012). Prevalence and predictors of vitamin D deficiency in non-supplemented women with systemic lupus erythematosus in the Mediterranean region: a cohort study. *Scand J Rheumatol*, 41(6), 472-475.
 24. Wright TB, Shults J, Leonard MB, et al. (2009). Hypovitaminosis D is associated with greater body mass index and disease activity in pediatric systemic lupus erythematosus. *J Pediatr*, 155(2), 260-265.

25. Toloza S, Cole D, Gladman D, et al. (2010). Vitamin D insufficiency in a large female SLE cohort. *Lupus*, 19(1), 13-19.
26. Souto M, Coelho A, Guo C, et al. (2011). Vitamin D insufficiency in Brazilian patients with SLE: prevalence, associated factors, and relationship with activity. *Lupus*, 20(10), 1019-1026.
27. Yeap S. (2013). Vitamin D levels: its relationship to bone mineral density response and disease activity in systemic lupus erythematosus patients on corticosteroids. *Int J Rheum Dis* 16, 11.
28. Borba V, Vieira J, Kasamatsu T, et al. (2009). Vitamin D deficiency in patients with active systemic lupus erythematosus. *Osteoporosis Int.* 20(3), 427-433.