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Clinical Pathology

Role of Vitamin D in Systemic Lupus Erythematosus Disease Activity

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ABSTRACT

Background: Systemic Lupus erythematous is systemic inflammatory disorder associated with immunological abnormalities that could affect many organs. Vitamin D has inhibitory properties on activity and multiplications of immune system cells associated with inflammation.

Aim of the work: To evaluate vitamin D level in systemic lupus erythematosus (SLE) cases, and to explore its variation in active state of the disease.

Patients and Methods: The study was done on 100 individuals in clinical pathology and rheumatology, rehabilitation and physical medicine departments at Al-AZHAR University Hospitals. Subjects classified into 2 groups. Group I included 70 systemic lupus erythematosus patients either in active or inactive state. Group II comprised 30 matched healthy subjects as regard age and gender. All participants were subjected to comprehensive clinical examination and recommended laboratory investigations.

Result: Vitamin D was significant low in systemic lupus erythematosus patients versus healthy control. Vitamin D level was statistically low in cases with active disease versus inactive disease. Statistical correlations were found between vitamin D level and activity index of the disease and laboratory markers indicating active state of the disease.

Conclusion: Vitamin D level inadequacy is a finding in systemic lupus erythematosus patients in active disease state. Vitamin D level could be a biomarker of disease activity.

Keywords: *Systemic Lupus Erythematosus (SLE); Vitamin D.*

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INTRODUCTION

Systemic lupus erythematosus is an autoimmune disease. Many environmental factors and many genes are involved in the pathogenesis of the disease. The disease is known to be associated with autoantibody production, dysfunction in of immune system and variable degree of inflammation that could affect more than one organ [1].

Environmental factors are assumed to share in clinical expression of the systemic lupus erythematosus diseases. Vitamin D level has been studied as one of the environmental factors. Vitamin D has an important role in various processes of the immune system, and its receptors were found on immune cells; macrophage, dentritic cells and lymphocytes. Immune cells are able to synthesize the active vitamin D metabolite. Vitamin D has the capability to modulate innate and adaptive immune responses [2].

Vitamin D deficiency is prevalent in SLE patients due to photosensitivity, renal impairment and the use of different drugs in treatment of the disease such as glucocorticoids which alter the metabolism and functions of vitamin D. [3]

PATIENTS AND METHODS

This work was done in Clinical Pathology and Rheumatology Departments at Al- AZHAR university hospitals (Al-Hussein and Bab El-Sharia). The study was conducted on 100 individuals. Subjects enrolled in the study were categorized into two groups (Patient and Control groups).

Patient group (Group I): includes 70 SLE patients. They were 62 females and 8 males. Their ages were 29.3±5.4 years. Their disease duration was from 2 - 10 years. Systemic lupus international collaborating clinics (SLICC) data were used to diagnose SLE disease [4]. Assessment of SLE activity was determined using the modified SLE disease activity index (SLEDAI). [5]

Exclusion criteria: Patients with other autoimmune diseases, chronic inflammatory diseases, systemic diseases (endocrine, cardiac, renal, hepatic, malignant) or under calcium or vitamin D therapy were excluded from the study.

The patient group was categorized retrospectively into: Active SLE patients, it comprised 44 SLE patients. They were 40 females and 4 males and inactive SLE patients

,it comprised 26 SLE patients. They were 22 females and 4 males.

Group II (Control group): 30 healthy individuals(matching cases as regard age and sex) were enrolled in the study as a control group.

Subjects involved in the study were informed orally about the procedures and gave written consent to share. The participants were subjected to thorough clinical examination and laboratory investigations.

The following laboratory investigations were done for all participants: Complete blood picture, erythrocyte sedimentation rate , C-reactive protein on automated spectrophotometry Au 480 system, USA, Complement C3 and C4 level , Anti-nuclear antibody (ANA) by immunofluorescence (IIF) technique, and by enzyme immunosorbent assay (ELISA) ,Anti- DNA by IIF technique on Crithedia Lucilia substrate, DiaSorin, Italy and by ELISA technique using Kit Invoa Diagnostics USA. Serum calcium (Ca), creatinine and urinary proteins of 24 hours by colorimetric assay using kits from Spinreact, Spain. Serum 25-hydroxychloecalciferol vitamin D 25(OH)D by ELISA technique Abcam, USA

Statistical Analysis:

Recorded data were analyzed using the statistical package of social science (SPSS) version 24 . Quantitative data expressed as Median (IQR) as the data was abnormally distributed. Qualitative data expressed as frequency and percentage. To compare between two means (for abnormal distributed data) Mann- Whitney test was used. To compare between non-parametric data Chi-square test was used. Kruskal Willis test (KW): when comparing more than two means (for abnormal distributed data). For correlating data Pearson's correlation coefficient test was used. Probability (P-value): P-value > 0.05 was considered insignificant, P- value < 0.05 was considered significant and P-value < 0.001 was considered highly significant.

RESULTS

Groups	Parameters	Cases	Control	MW	P-value
Hemoglobin (g/dl)	Median	10	11.9	0.0	< 0.001
	IQR	9 - 10	11.8 - 12.7		
PLTs (x10³/ul)	Median	180	205	602.5	0.001
	IQR	160 - 203	179.8 – 230		
24 h urine protein (mg/24h)	Median	68	35.5	315	< 0.001
	IQR	50 - 835	21.5 - 70.3		
Creatinine (mg %)	Median	0.80	0.6	571.5	< 0.001
	IQR	0.60 - 0.90	0.5 - 0.7		
Ca (mg/dl)	Median	8.45	8.7	651	0.003
	IQR	8 - 8.9	8.5 - 9.02		
ESR (mm/h)	Median	39	7	0.0	< 0.001
	IQR	28 - 47	6 - 9		
ANA titer (U/ml)	Median	80	9.5	10.5	< 0.001
	IQR	68 - 100	7 - 15.3		
Anti-DNA titer (U/ml)	Median	340.5	59.5	0.0	< 0.001
	IQR	232.8 - 415	35.3 - 70.3		
C3 (mg/dl)	Median	110	158	32	< 0.001
	IQR	100 - 131.3	149 - 168		
C4 (mg/dl)	Median	16	38.5	0.0	< 0.001
	IQR	10 - 20	36 - 41.3		

MW: Mann Whitney U test.

Table 1: Comparison between patient and control group as regard studied laboratory data.

There was statistical significant decrease in platelet count and serum calcium (ca) in cases group compared to control group. There were highly statistical decrease in hemoglobin level, complement C3 and complement C4 in cases group versus control group. There was highly statistical increase in 24 hours total urinary proteins, serum creatinine, erythrocyte sedimentation rate , ANA and anti- DNA in cases group versus control group.

Vitamin D	Groups	Cases (N = 70)		Control (N = 30)		Stat. test	P-value
Vitamin D (ng/ml)	Median	9		36		MW = 80.5	< 0.001 HS
	IQR	7 - 16		25.8 - 46.5			
Vitamin D Status	Sufficient	0	0%	17	56.7%	X^2 = 53.9	< 0.001 HS
	Insufficient	14	20%	8	26.7%		
	Deficient	56	80%	5	16.7%		

Table 2: Comparison between patients and control group as regard vitamin D.

There was highly statistical significant decreased vitamin D in cases group versus control cases.

Parameters	Groups	Inactive (N = 26)	Active (N = 44)	test	P-value
Hemoglobin (gm %)	Median	10.10	9.75	MW =406	0.043 S
	IQR	9.30 - 10.8	9 - 10.3		
24 h urine protein (mg/24 h)	Median	52.5	760	MW =214	< 0.001 HS
	IQR	39 - 67	60.5 - 995		
Creatinine (mg %)	Median	0.7	0.90	MW =317.5	0.002 S
	IQR	0.5 - 0.8	0.70 – 1.0		
ESR (mm/h)	Median	27	45	MW =3.5	< 0.001 HS
	IQR	23 - 30	40 - 52		
ANA titer (U/ml)	Median	66.5	97	MW = 61	< 0.001 HS
	IQR	37.5 - 69.3	80.3 - 107.3		
ANA IIF	Negative	7 26.9%	0 0%	X^2 = 23.8	< 0.001 HS
	1/40	19 73.1%	25 56.8%		
	1/80	0 0%	19 43.2%		
Anti-DNA titer (U/ml)	Median	205	410	MW = 0.0	< 0.001 HS
	IQR	150 - 239.3	350 - 555.5		
Anti-DNA IIF	1/40	26 100%	8 18.2%	X^2 = 43.8	< 0.001 HS
	1/80	0 0%	19 43.2%		
	1/160	0 0%	17 38.6%		
C3 (mg/dl)	Median	135.5	100	MW = 0.0	< 0.001 HS
	IQR	130 - 140	88.5 - 109.8		
C4 (mg/dl)	Median	20.5	12	MW = 32.5	< 0.001 HS
	IQR	20 - 26	9 - 15		

Table 3: Comparison between active versus inactive SLE patients as regard studied laboratory data.

There was statistical significant decrease in hemoglobin level and statistical significant increase in serum creatinine level in active SLE patients versus inactive SLE patients. There was highly statistical significant increase in 24 hours total urinary proteins, ESR, ANA done by ELISA and done by IIF, anti-DNA done by ELISA and done by IIF technique in active SLE cases versus inactive SLE cases. There were highly statistical significant decrease in serum level of complement C3 (C3) and complement C4 (C4) in active SLE versus inactive SLE group .

Vitamin D	Groups	Activity		Stat. test	P-value
		Inactive (N = 26)	Active (N = 44)		
Vitamin D (ng/ml)	Median	17	7	MW = 0.0	< 0.001 HS
	IQR	14.8 - 23	7 - 9		
Vitamin D Status	Insufficient	14 53.8%	0 0%	X^2 = 29.6	< 0.001 HS
	Deficient	12 46.2%	44 100%		

Table 4: Relation between vitamin D and activity in cases group.

There was highly statistical significant decreased vitamin D level in active SLE patients versus inactive SLE patients.

Variables	Vitamin D	
	r	p-value
Duration of disease	- 0.37	0.001
DAI	- 0.915	< 0.001
PLT	0.319	0.007
24 hour urine proteins	- 0.573	< 0.001
Creatinine	- 0.415	< 0.001
Erythrocyte sedimentation rate	- 0.724	< 0.001
ANA	- 0.734	< 0.001
Anti ds-DNA Titer	- 0.778	< 0.001
Complement C3	0.752	< 0.001
Complement C4	0.752	< 0.001

Table 5: Vitamin D correlations with DAI and other data in cases group.

There was highly statistical negative correlation between vitamin D and index of disease activity (DAI), creatinine, ESR, ANA titer, anti-DNA titer and 24 hour urine protein. There was significant correlation between vitamin D level and disease duration. There was statistically positive correlation between vitamin D and PLTs. There were statistical correlation between vitamin D and C3 & C4.

DISCUSSION

Measurement of Systemic lupus Erythematosus disease activity is central to evaluate outcomes, differentiate between SLE patients, response to therapy and to improve morbidity and mortality rate

of SLE disease. Fluctuation levels of disease activity are present among systemic lupus erythematosus patients. As there is no standard laboratory marker that properly reflect disease activity many composite clinical indices have been developed for the evaluation of disease activity [6,7].

25 hydroxycholecalciferol (25 (OH) vitamin D is the main circulating form of vitamin D. 25 (OH) vitamin D reflects vitamin D supply to the body from skin synthesis and nutritional intake. It has been found that many immune cells express both vitamin D receptor and 1α, hydroxylase needed for synthesis of the active form of vitamin D with potential of autocrine or paracrine effect in additional to endocrine effect. Vitamin D has inhibitory properties on cell proliferation, anti-inflammatory and immunomodulation. Vitamin D inadequacy could direct the immune system to a loss of tolerance. Supplementation of vitamin D could be of great value in patients with lupus [3,8].

The target of this study was to evaluate vitamin D level in Egyptian patients with SLE disease and to explore if it could be used as a biomarker reflecting the degree of disease activity.

Vitamin D inadequacy could be present in healthy populations. In our study 43.4% of control group showed inadequate vitamin D levels [16.7% deficient and 26.7% insufficient]. This finding is going with *Squance and coworkers.* [9] *and Khairallah and coworkers.* [10].

In our work, in SLE group, 80% showed deficient level, 20% showed insufficient level and 0% showed normal vitamin D level. There was statistical significant decrease in vitamin D in SLE group versus control group. This finding despite sunny days are present most of the year in Egypt. This is going with *Korah and coworkers* [11], *Elsaid and coworkers* [12] *and Khairallah and coworkers.* [10]. Other authors reported 25(OH) vitamin D inadequacy in up to 90% of SLE cases in Saudi Arabia; 82% Norway 71% Poland. However much lower rates have been reported in other studies 18% Canada, 27%. Hong Kong 20% United Status and 15% Spain [13]. They explained lower levels and high prevalence of vitamin D inadequacy as most patients are females with low outdoor activities or due to clothing, lower body surface area and hormonal effects. Other contributing factors could be lupus nephritis due to decrease 1 α hydroxylase activity, usage of drugs as glucocorticoids, hydroxychloroquire and anticonvulsants that enhance vitamin D catabolism and the presence of vitamin D antibodies that probably enhance vitamin D clearance.

In our study, vitamin D in active SLE group was statistically low versus inactive SLE group. There were statistical correlation between vitamin D and activity index of the disease . These findings going with *Yap and coworkers.* [14], *Zheng and coworkers.* [15] *and Khairallah and coworkers* [10]. So vitamin D inadequacy could predict SLE disease activity. This finding is expected due to the immunosuppressive and the anti-inflammatory properties of vitamin D. The inflammatory process in SLE enhance vitamin D catabolism [Bidirectional relationship]. This finding contradictory to other studies [16].The conflicting results could be due to diverse study populations, the retrospective nature of the study, methodological variations, statistical power differences between studies and heterogeneity of treatment.

Anti-ds-DNA antibody is specific for SLE and its level fluctuates with disease activity. In this study, DNA antibodies were statistically high in active SLE group versus inactive SLE group. There were highly statistical correlation between vitamin D levels and anti-ds-DNA levels. This finding going with *Mok and coworkers.* [17], *Attar and Siddiqui* [13] *and Nerviani et al.*[18], but was in disagreement with *Khairallah and coworkers.* [10].

In our study, both complement C_3 and complement C_4 were statistically low in active SLE group versus inactive SLE group. There were highly statistical correlation between vitamin D levels and C_3 and C_4 levels. These findings are in agreement with study done by *Giles and Boackle* [19], but contradictory to studies done by *Attar and Siddiqui*[13] who found correlation between vitamin D and C_4 only. They explained this finding by the fact that in SLE the main triggering of complement activity is mediated mainly by the classical pathway. In addition our findings were contradictory to study done by *Khairallah et al.*[10]. These conflicts between studies could be due to variations in the compensatory effect of the liver between populations, variation in DAI, heterogeneity of drugs used for treatment of SLE and difference in method of assay.

In our study, ANA test was positive in 73.1% in inactive SLE group but was 100% positive in active SLE group. The level of ANA was statistically high in active SLE group versus inactive SLE group. There were statistical correlation between vitamin D level and ANA levels. On contrary *Squance et al.* [9] did not find any correlation between vitamin D and ANA levels. They stated that 2 steps are needed to develop SLE overt disease. The first step is the conversion from tolerance to benign [serological] autoimmunity. Vitamin D levels have impact upon this step. The second step is the conversion from serological SLE to overt SLE disease. Other factors [environmental or hormone] could trigger this step 2. So vitamin D deficiency may predispose to disease expression without influencing its severity or behavior once established.

In our study ESR levels were statistically high in SLE group versus control group. ESR was found significantly high in active SLE group versus inactive SLE group. There were significant correlation between vitamin D levels and ESR levels. These findings are going with studies done by *Miskovic and coworkers.* [20] who explained this fact due to the effect of cytokines in the induction of acute phase reactant.

CONCLUSION

Vitamin D is statistically decreased in SLE patients versus healthy individuals and showed more significant decrease in active SLE versus inactive SLE patients. So vitamin D level could predict the activity state of the disease in patients with systemic lupus erythematosus.

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