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Body Mass Index in Systemic Lupus Erythematosus: Relation to Disease Activity, Bone Mineral Density And Vitamin D Level

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ABSTRACT

Background: High incidence of obesity has been reported in Systemic Lupus Erythematosus (SLE). However, the relationship between obesity and SLE is still unclear. Studies reported low vitamin D levels and bone mineral density (BMD) in SLE patients. Moreover, vitamin D plays a vital role in the pathogenesis and complication of SLE.

Objective: To investigate the link between increased body mass index (BMI), disease activity, BMD, and vitamin D level in SLE patients .

Patients and Methods:120 SLE patients were classified according to BMI into three groups, normal BMI (<25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (>30 kg/m^2). Laboratory investigations were done, assessment of disease activity by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), measuring the serum levels of 25-hydroxyvitamin D 25(OH) D were assessed.

Results: 30% were overweight, and 45% were obese. Overweight and Obese patients had lower 25(OH) D levels and a high prevalence of osteoporosis in comparison to patients with normal BMI. SLEDAI score was positively correlated to BMI and negatively correlated with 25(OH) D and BMD.

Conclusion: Increased BMI is common in SLE and is independently associated with higher disease activity, osteoporotic rates, and lower 25 (OH) vitamin D levels. These findings are associated with important clinical implications, which suggests that weight control may be a potential target for improving SLE outcome.

Keywords: Bone mineral density, Obesity, Systemic Lupus Erythematosus, Vitamin D.

INTRODUCTION

Obesity could modify the chronicity and severity of various autoimmune pathologies, through the release of pro-inflammatory cytokines which are incorporated in the onset and progression of diverse autoimmune diseases, like rheumatoid arthritis, psoriatic arthritis, and multiple sclerosis[(1)]. Studies reported a high predominance of obesity in Systemic Lupus Erythematosus (SLE) ranges between 29 and 50 percent [(2)].

Reports noticed that obese SLE patients have increased gene and protein expression of various pro-inflammatory cytokines as IL-23 [(3)], and TNF-α, which linked to total fat mass [(4)]. Obesity is a state of chronic low-grade inflammation, associated with altered immune function and the release of different adipokines such as leptin [(5)].

Elevated leptin levels were detected in SLE patients and could be the connection between both obesity and SLE [(6-7)]. Obesity aggravates the inflammatory burden of SLE disease, and contributes to increased cardiovascular disease risk [(8)]. Obese SLE patients are presented with higher disease activity, more depressive symptoms, and fatigue in comparison to non-obese SLE patients[(9)].

Vitamin D is recognized as an immune modulator that regulates innate and adaptive immune response in the presence of vitamin D receptor (VDR) on the surface of natural killer cells, antigen-presenting cells, and B- and T-lymphocytes [(10)].

Studies demonstrate low BMD and vitamin D in SLE patients. An inverse association was observed between SLE disease activity and vitamin D serum level. Moreover, low serum vitamin D levels are combined with poor outcomes in SLE patients including fatigue, cardiovascular diseases, cutaneous, and renal involvement[(11)].

In this study, we aimed to study the association between increased BMI and disease activity, BMD and vitamin D level in a cohort of SLE patients.

PATIENTS AND METHODS

The present cross-sectional study enrolled 120 adult SLE patients who were divided into three groups according to BMI based on WHO international classification [(12)]. **Group I** included 30 (25%) SLE patients with normal weight (BMI < 25 kg/m^2), **Group II** included 36 (30%) SLE patients with overweight (BMI: 25 – 29.9 kg/m^2) and **Group III** included 54 (45%) patients with obesity (BMI ≥ 30 kg/m^2). Patients were recruited from the Department of Rheumatology and the Department of Physical Medicine, Rheumatology, and Rehabilitation including the Obesity Unit Clinic from May 2018 to September 2018.

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The diagnosis of SLE was based on the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for systemic lupus erythematosus [13]. SLE disease activity was determined by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [14]. Grades of activity classified as follows: No activity (SLEDAI =0), mild activity (SLEDAI =1-5), moderate activity (SLEDAI =6-10), severe activity (SLEDAI =11-19), very highly activity (SLEDAI> 20) [15]. Patients with a history of chronic or inflammatory diseases that affects the absorption of vitamin D, renal stones, calcium metabolism disorder, liver cirrhosis, malignancy, myocardial infarction, and hospitalization because of the complications of SLE during the study and postmenopausal women were excluded. Drug history of all patients was taken as long-term steroid use more than 60 days and immunosuppressive drugs like Azathioprine (AZA) or antimalarial agents as Hydroxychloroquine (HCQ) and Mycophenolatemofetil (MFM**).**

Ethical approval:

The study was approved by the Ethical Committee of Ain Shams University (IRB number 000017585), and all patients signed informed consent before participation.

Laboratory Analyses:

Blood samples were collected for a complete blood cell count (CBC), determination of kidney and liver function tests, C-reactive protein (CRP), Westergren erythrocyte sedimentation rate (ESR) and urine samples were obtained for spot urine protein to creatinine ratio (P/C).

Anti-dsDNA antibodies were also measured using the enzyme-linked immunosorbent assay (ELISA) technique (Quanta Lite, ™ds-DNA Kit, INOVA Diagnostic Inc, CA, USA), and were measured in IU/mL. Anti-dsDNA tests were classified as negative if the level was between 0-200 IU/mL; equivocal if the level was between 201-300 IU/mL; and positive if the level was above 301 IU/mL. Complement components 3 and 4 (C3) and (C4) were measured by nephelometry (Behring Nephelometer II, Dade Behring, Marburg, Germany), and antinuclear antibodies (ANA) were measured by ELISA.

Bone metabolites were assessed including total serum calcium, serum phosphorus, serum alkaline phosphatase, and serum levels of 25-hydroxy vitamin D and parathyroid hormone (PTH) were quantitatively measured by ELIZA assay in serum.

The level of serum 25-hydroxyvitamin D 25(OH)D was measured using ELISA technique (K2110, immunodiagnostic [Dutch Company], Holland). Vitamin D deficiency was defined as follows:-

(1) Serum level of 25(OH)D level less than 10 ng/ml: severe vitamin D deficiency.
(2) Serum level of 25(OH)D level between 10 and 30 ng/ml: insufficiency in vitamin D.
(3) Serum level of 25(OH)D level more than 30 ng/ml: normal range.

Bone mineral density assessment (BMD):

Bone mineral density (BMD) of the lumbar vertebrae and femoral necks were measured with dual-energy X-ray absorptiometry, and patients were stratified as normal and abnormal BMD groups (including osteopenia and osteoporosis). This was performed by GE LUNAR DXA apparatus made in Madison, USA. Bone mass was expressed using T score according to WHO criteria: (1) Osteoporosis was defined as T score less than −2.5. (2) Osteopenia was defined as T score from −1.5 to <2.5. (3) Normal more than −1.0 [16].

Statistical analyses

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described using their means and standard deviations, range, median and interquartile range (IQR). Categorical variables were described using their absolute frequencies and were compared using Chi square test when appropriate. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. To compare means of more than two groups, one way ANOVA test (used with normally distributed data) was used.

To compare medians of more than two groups, Kruskal Wallis test (used with not normally distributed data) was used. Least significant difference (LSD) was used as a post-hoc test for multiple comparisons among the studied groups when F was significant. Spearman rank correlation coefficients was used to assess strength and direction of a linear relationship between two variables. The level of statistical significance was set at 5% ($P<0.05$). Highly significant difference was present if $p\leq0.001$.

RESULTS

One hundred and twenty patients with SLE (110 women and 10 men) were studied. Their age ranged from 22 to 45 years with a mean age of 34.14 (± 6.1 years). The average SLEDAI score ranged from 0 to 14 with a mean of 3.53 (±3.6). Regarding disease activity, (20%) of patients had mild activity, (48.3%) had moderate activity, while (26.7%) had severe activity. The average BMI was (29.37 ± 6.46), (30%) of patients were over-weight, while (45%) were obese.

Table 1 shows the characteristics of the three studied groups. ESR was higher in the overweight and normal-weight compare to the obese group. Regarding patients' treatment, a significant increase in azathioprine was found in overweight and obese groups compared to the normal weight group. There was a statistically significant relationship between BMI categories and the use of hydroxychloroquine. The difference was significant between normal and obese groups (Table 1).

Table (1): Demographic features, laboratory investigations and medications received in systemic lupus erythematosus patients' groups based on body mass index

Variable	Normal group (30)	Overweight group (36)	Obese group (54)	P	LSD/Pairwise comparison
	Median (IQR)	Median (IQR)	Median (IQR)		
Age (years): Mean ± SD	34.6 ± 5.222	34.67 ± 4.367	35.85 ± 4.388	0.550¥	
Gender: Female Male	27 (90%) 3 (10%)	33 (91.7%) 3 (8.3%)	5(96.3%) 2 (3.7%)	0.580∞	
Disease Duration (year)	5	5	3	0.346#	
ESR (mm/h)	25	40	20	0.007*#	P1 0.3 P2 0.008* P3 0.895
CRP (mg/dL)	8	9	7	0.066#	
ANA titer	0.0028	0.0017	0.0017	0.116#	
C3 (mg/dL): Mean ± SD	97.33 ± 14.849	84.39 ± **13.626**	104.07 ± 13.365	0.008*	P1 0.011* P2 0.001* P3 0.674
C4 (mg/dL)	17	17	22	0.001*	P1 >0.999 P2 0.011* P3 0.005*
Serum Ca (mg/dL) **Mean ± SD**	9.427 ± 0.483	9.383 ± 0.375	9.352 ± 0.48	0.767¥	
Serum Phosphorus (mg/dL): **Mean ± SD**	3.567 ± 0.389	3.483 ± 0.407	3.452 ± 0.479	0.513¥	
Alkaline phosphatase (U/L) **Mean ± SD**	96.87 ± 13.249	91.11 ± 17.511	82.89 ± 12.839	0.683¥	
Vitamin D (ng/dL) **Mean ± SD**	25.33 ± 4.599	24.67 ± 3.163	23.22 ± 3.892	0.387¥	
Anti-ds-DNA (+ve) N (%)	24 (80%)	28 (77.8%)	44 (81.5%)	0.823∞	
Steroid duration (month) **Cumulative steroid dose (gm)**	60 36	60 36.375	42 30.3	0.373# 0.447#	
Immunosuppressive use: Yes n (%)	18 (60%)	32 (88.9%)	44 (81.5%)	0.014*∞	
Azathioprine Users n(%) **Mycophenolate mofetil Users n (%)**	16 (46.7%) 2 (6.7%)	30 (83.3%) 2 (5.6%)	44 (77.8%) 0 (0%)	0.044*∞	P1 0.612 P2 0.174 P3 0.081
Hydroxychloroquine Users n (%)	30 (100%)	32 (88.9%)	46 (85.2%)	0.022*∞	P1 0.12 P2 0.756 P3 0.046*

#Kruskal - Wallis test, ∞Chi-square test, ¥F One way ANOVA test, *p<0.05 is statistically significant

P_1 Difference between normal and overweight groups P_2 Difference between overweight and obese groups P_3 Difference between normal and obese groups

BMI: Body mass index, **ESR:**erythrocyte sedimentation rate, **CRP:** C-reactive protein, **ANA:**antinuclear antibodies, **C3:**complement 3, **C4:** complement 4 , **Ca:** Calcium **Anti-ds-DNA**: anti-double stranded- DNA

A highly significant increase in SLEDAI score and SLEDAI score grades was found in overweight and obese groups compared to the normal weight group. Severe activity was present in 44.4% of obese patients versus 5.6% of overweight ones. A significant increase in the prevalence of osteoporosis at T-score in obese groups; compared to the normal weight group (table 2).

Table (2): Disease activity and bone mineral density in systemic lupus erythematosus patients' groups based on body mass index

Variable	Normal group (30)	Overweight group (36)	Obese group (54)	P	Pairwise comparison
	Median (IQR)	Median (IQR)	Median (IQR)		
SLEDAI Score	2	4	2	0.001# *	P1 0.074 P2 <0.001* P3 0.641
SLEDAI severity				0.002*∞	P1 0.08 P2 0.001* P3 0.125
Severe activity N(%)	6 (20%)	2 (5.6%)	24 (44.4%)		
Moderate activity N (%)	18 (60%)	20 (55.6%)	20 (37%)		
Mild activity N(%)	4 (13.3%)	12 (33.3%)	8 (14.8%)		
No activity N(%)	2 (6.7%)	2 (5.6%)	2 (3.7%)		
Osteoporosis rate (T-score)				0.033*∞	P1 0.177
Normal N(%)	19 (63.3%)	14 (38.9%)	16 (29.6%)		
Osteopenia N(%)	5 (16.7%)	14 (38.9%)	19 (35.2%)		P2 0.481
Osteoporosis N(%)	6 (20%)	8 (22.2%)	19 (35.2%)		P3 0.011*

SLEDAI*:* Systemic Lupus Erythematosus Disease Activity Index, #Kruskal - Wallis test, ∞Chi-square test *p<0.05**.**
SLEDAI*:* Systemic Lupus Erythematosus Disease Activity Index, #Kruskal - Wallis test, ∞Chi-square test *p<0.05 is statistically significant.

P_1 Difference between normal and overweight groups P_2 Difference between overweight an obese groups P_3 Difference between normal and obese groups

There was a statistically significant difference regarding vitamin D level between the obese group and the other 2 groups (table 3).

Table (3): Relation between vitamin D level and BMI of the studied patients

	Normal group N=30(%)	Overweight group N=36(%)	Obese group N=54(%)	P	Pairwise comparison
Deficiency	0 (0)	0 (0)	0 (0)		P1 0.746
Insufficiency	18 (60)	23 (63.9)	45 (83.3)	0.015*	P2 0.035*
Sufficiency	12 (40)	13 (36.1)	9 (16.7)		P3 0.017*

*p<0.05 is statistically significant

In addition, age, SLEDAI score, serum C3, and C4 were found to have a highly significant positive correlation with BMI (Table 4).

Table (4): Correlation analysis for baseline clinical, laboratory, treatment and BMD data associated with BMI

Associated Factor		BMI	
		r	P
Clinical data	**Age** (years)	0.211	**0.021***
	SLEDAI score	0.196	**0.032***
	Duration (year)	-0.081	0.378
	ESR (mm/h)	-0.087	0.342
	CRP (mg/dL)	-0.129	0.162
	ANA titer	-0.063	0.501
	C3 (mg/dL)	0.182	**0.047***
	C4 (mg/dL)	0.285	**0.002***
	Ca (mg/dL)	-0.035	0.704
	Phosphorus (mg/dL)	-0.106	0.249
	Alkaline phosphatase (U/L)	-0.141	0.123
	Vitamin D (ng/dL)	-0.126	0.170
Treatment data	**Steroid duration** (month)	-0.074	0.419
	Cumulative steroid dose (gm)	-0.105	0.253
	T-score (Neck Femur)	0.171	0.062
	T-score (Lumbar Spine)	0.051	0.581

r Spearman rank correlation coefficient SLEDAI: *Systemic Lupus Erythematosus Disease Activity Index,* , **ESR** :erythrocyte sedimentation rate, **CRP**: c-reactive protein, ANA: antinuclear antibodies, **C3**:complement 3, **C4**: complement 4 , **Ca:** Calcium, *p<0.05 is statistically significant

There was a statistically significant positive correlation between SLEDAI score and BMI. On the other hand, there was a significant negative correlation between SLEDAI score and all of C3, alkaline phosphatase, and 25(OH) D. SLEDAI score was significantly negatively correlated with T score of both femur neck and lumbar spine (Table 5).

Table (5): Correlation analysis for baseline clinical, laboratory, treatment and BMD data associated with SLEDAI

Associated Factor		EDAI	
		r	P
Clinical data	**Age** (years)	-0.058	0.533
	BMI (kg/m^2)	0.196	0.032*
	Duration (year)	0.004	0.962
	ESR (mm/h)	0.124	0.176
	CRP (mg/dL)	0.076	0.409
	ANA titer	-0.063	0.501
	C3 (mg/dL)	-0.239	0.008*
	C4 (mg/dL)	-0.144	0.117
	P/C ratio	0.076	0.407
	Ca (mg/dL)	0.045	0.623
	Phosphorus (mg/dL)	0.132	0.151
	Alkaline phosphatase (U/L)	-0.181	0.048*
	Vitamin D (ng/dL)	-0.307	0.001**
Treatment data	**Steroid duration** (month)	-0.021	0.82
	Cumulative steroid dose (gm)	0.003	0.978
	T-score (Neck Femur)	-0.262	0.004*
	T-score (Lumbar Spine)	-0.215	0.018*

r Spearman rank correlation coefficient SLEDAI: *Systemic Lupus Erythematosus Disease Activity Index,*
ESR :erythrocyte sedimentation rate, **CRP**: c-reactive protein, ANA: antinuclear antibodies, **C3**:complement 3, **C4**: complement 4 , **Ca:** Calcium, *p<0.05 is statistically significant.

DISCUSSION

Obesity has been described as a state of chronic, low-grade inflammation that is mediated by adipocytes producing cytokines, including TNF-alpha, IL-6, IL-8, and monocyte chemoattractant protein -1(MCP-1). Production of such cytokines is the trigger for subsequent activation of the inflammatory cascade and autoimmunity[17].

In this study, 30% were overweight and 45% were obese which is consistent with that in previous studies. One study reported a 39% prevalence of obesity among a cohort of women with lupus [18] and the study of **Katz *et al.*** [19] showed a prevalence of 29– 50%.

In the present study SLEDAI score was positively correlated with BMI. This also was reported by **Patterson *et al.*** [9] who found that obesity was independently linked to worse patient-reported outcomes, including disease activity and symptoms of depression, pain, and fatigue In addition a high BMI in SLE patients was associated with more cognitive and renal affection [20]. Similarly, **Teh *et al.*** [21] revealed that an increased BMI was complicated by worsening of disease activity as evaluated by SLEDAI score. So increase BMI in SLE patients could worsen the chronic inflammatory status, increasing the oxidative stress and increase the secretion of pro-inflammatory cytokines [1].

Our study demonstrated that 25(OH) D levels were lower in obese and overweight in comparison to normal-weight SLE patients. Similarly, previous studies demonstrated an increased prevalence of vitamin D deficiency among SLE patients [22].

Vitamin D deficiency is highly predominant in SLE patients as patients with SLE usually avoid the sun due to photosensitive rashes and the potential for disease flare [23]. Also, lupus nephritis is associated with a decreased 1-alpha-hydroxylase activity on 25(OH)D, and a subsequent decrease in 1,25(OH) 2D production and presence of vitamin D autoantibodies leading to its clearance [24].

Moreover, obesity is considered a risk factor for vitamin D deficiency as adipose tissue acts as the sinkhole for vitamin D [25]. Also, SLE patients with high BMI usually have a high body fat content which acts as a reservoir for lipid-soluble vitamin D. At the same time, the release of vitamin D from fat is extremely slow and is proportional to vitamin D concentration in the adipose tissue to protect the body from toxic effects of active forms of vitamin D. Thus, excess body fat results in increased sequestration and low availability of vitamin D, leading to low serum 25(OH) D levels [26].

Indeed, it was found in previous studies that serum level of 25(OH) D is inversely associated with BMI, fat mass, and waist circumference [27-28]. This inverse correlation is also detected in the present study but it doesn't reach a significant level.

We found a negative correlation between SLEDAI score and 25(OH) D levels. Similarly, vitamin D deficiency among SLE patients was demonstrated and its connection to complications of the disease and disease severity was shown[29]. This could be attributed to increased levels of memory B lymphocytes, which may increase SLE disease activity [30].

Vitamin D has a protective role through inhibition of differentiation of T helper 1- lymphocytes, T helper 17 lymphocytes, stimulation of T regulatory cells, inhibition of B cell proliferation, and decrease the production of autoantibodies[31].

The prevalence of osteoporosis at T-score was higher in our overweight and obese groups of SLE patients compared to the normal-weight group. Similarly, studies revealed a high prevalence of osteoporosis in SLE patients [32-33].

BMD usually decreases among SLE patients. This could be attributed to multifactor as elevated inflammatory cytokines, hormonal imbalance, renal impairment, metabolic, and medications as a corticosteroid [34-35].

In this study, BMI was not correlated with BMD but the SLEDAI score was negatively correlated with 25(OH) D levels and BMD (T-score of neck Femur and T-score of the lumbar spine). Regarding our patients' treatment, a significant increase in azathioprine was found in overweight and obese groups as compared to the normal-weight group. This could be explained by the fact that obese SLE patients have the more active disease which demands the use of more immunosuppressive drugs like corticosteroids and AZA which could accelerate 25(OH) D metabolism and reduce vitamin D and BMD [27].

In conclusion, we observed that increased BMI is common in SLE patients and is independently associated with higher disease activity, higher osteoporotic rates, and lower serum 25 (OH) vitamin D levels.

These findings highlight the need for weight control and lifestyle interventions targeting lupus patients with overweight as obesity may represent a modifiable target for improving outcomes among obese SLE patients. Furthermore, routine assessment of vitamin D levels and BMD in SLE especially those presented with increased BMI is also highly recommended.

Finally, the cross-sectional design of our study limits us by simply showing an association between obesity and SLEDAI, serum 25 (OH) vitamin D level, and BMI but not causality. Prospective studies are needed for further evaluation. long prospective studies on the effect of bodyweight reduction on SLE activity and vitamin D level .

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