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Frequency of Low Bone Mineral Density and Osteoporosis in a Cohort of Egyptian patients with Systemic Lupus Erythematosus

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ABSTRACT
Background: several studies have found an increase in bone loss and risk of fracture in patients with systemic lupus erythematosus. **Objectives:** To determine the frequency of low bone mineral density and osteoporosis in a cohort of Egyptian patients with systemic lupus erythematosus and their relation to disease activity. **Patients and Methods:** This is a cross sectional study which was carried out on 60 patients fulfilling SLICC classification criteria for systemic lupus erythematous. All patients were attending the Rheumatology Outpatient Clinic and Internal Medicine and Rheumatology Inpatient Department at Ain Shams University Hospital from April (2016) to august (2016). **Results**: Mean values of lumbar spine, femoral neck BMD were 1.0 ± 0.15 and 0.9 ± 0.15 g/cm2, respectively, with mean T-score values at each site of -1.4 ± 1.3 and -0.8 ± 1.0, the frequency of osteopenia among the studied 60 SLE patients was 40.0% and the frequency of osteoporosis was 25.0%. **Conclusion:** We found that there is increased frequency of low bone mineral density and osteoporosis among SLE patients.
Keywords: Systemic lupus erythematosus, bone mineral density, frax.

INTRODUCTION
Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that often affects young women [(1)]. It is characterized by periods of acute exacerbations that can affect any organ system [(2)].SLE is associated with significant comorbidities which can impair quality of life. SLE is also associated with increased rates of infection and increased risk of atherosclerosis and cardiovascular diseases [(3)]. The risk of malignancy in people with SLE is controversial [(4)].

Recent studies have highlighted the high prevalence of osteoporosis and bone fractures in a relatively young population of patients suffering from SLE [(5)].The etiology of reduced bone mass in SLE is multifactorial and includes a variety of intrinsic factors to the disease itself and treatments side effects [(6)]. Older age, postmenopausal status, smoking, disease duration, glucocorticoid (GC) treatment, renal insufficiency, Raynauds syndrome, lupus anticoagulant and reduced BMD have all been reported as risk factors of osteoporosis and fractures in SLE [(7)].SLE itself may result in low BMD, especially in patients with high systemic lupus erythematosus disease activity index (SLEDAI)[(8)]. However, some recent studies have shown that there are no predictors of bone loss in relation to the disease activity [(6)].

Although BMD from DXA is widely used for fracture prediction, its accuracy is Limited [(9)]. Fracture risk assessment tool (FRAX) is used for estimation of individualized 10-year probability fracture [(10)]. The use of this tool has been shown to enhance prediction of hip fractures and other major osteoporotic fractures over the use of BMD alone especially in SLE patients [(11)].

AIM OF THE STUDY
To determine the frequency of low bone mineral density and osteoporosis in a cohort of Egyptian patients with systemic lupus erythematosus and their relation to disease activity.

PATIENTS AND METHODS
A) Patients:
This is a cross sectional study which was carried out on 60 patients fulfilling SLICC classification criteria for systemic lupus erythematous [(12)].

Exclusion Criteria
Patients below 40 years of age and above 50 years of age, Postmenopausal females, SLE patients with a history of previously diagnosed osteoporosis, Patients receiving treatment for osteoporosis, Patients with diabetes mellitus and chronic kidney diseases (not SLE related), Patients with other co-existing autoimmune diseases or metabolic bone diseases and Smokers and alcohol consumers.

Ethical issues
An informed consent had been obtained from each participant in the study and the approval of the Ain Shams medical ethical committee had been obtained. All patients were subjected to the following: Full history taking including: SLE

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duration in years, drugs in use, smoking, alcohol intake, menstrual history, diabetes mellitus (DM). Thorough clinical examination including: Blood pressure, body mass index (BMI) and rheumatological examination. In addition to assessment of SLE disease activity SLEDAI.

b) METHODS

Laboratory assessment

Routine biochemistry blood tests were done. Complete blood count using with automated cell counter, ESR by the Westergren method C-reactive protein (CRP) with titer by ELISA. Urine analysis, protein/creatinine ratio, liver function tests , liver enzymes including (ALT, AST, total bilirubin and serum albumin, PT), serum calcium (Ca++), phosphorus(PO4---) and alkaline phosphatase (AlkP). Anti-nuclear antibody (ANA) by ELISA, anti-dsDNA antibody by immunofluorescence and serum complement fixation test (C3 and C4) levels by radial immunodiffusion assay.

Bone mineral density measurement using Dual Energy Absorptiometry (DXA):

The equipment used to measure bone mineral density (BMD) in this study was the GE-Lunar DXA bone densitometry. Bone was measured at the hip region and at the lumbar spine from L1 to L4.Results were compared to and plotted against the peak reference of young adults (T-score). Following the WHO classification for osteoporosis subjects were divided into: Patients with BMD below 2.5 standard deviations and a history of fracture were considered to have established osteoporosis. Patients with BMD below 2.5 standard deviations and below young adult reference that denoted osteoporosis. Patients with BMD range from 1 to 2.5 standard deviations were considered to have osteopenia. Patients with BMD above 1.0 standard deviation are considered normal [(13)].

Fracture risk assessment using FRAX tool

BMI-based FRAX score was calculated on a computer format for patients' ≥ 40 years of age (http://www.shef.ac.uk/FRAX).

This algorithm allows to estimate the 10-year probability of major osteoporotic fractures (which include hip, clinical spine, humerus, and forearm fractures) and of only hip fractures, by recording information about: Age, sex, body mass index (BMI), prolonged corticosteroid therapy, rheumatoid arthritis, secondary osteoporosis, previous fragility fracture, smoking, alcohol abuse, parental history of hip fracture, measurement of femoral neck BMD T-score [(14)]. Elevated 10-year probability score was defined according to National Osteoporosis Foundation as 3% or more for hip fracture and 20% or more for major osteoporotic fracture [(15)].

The study was approved by the Ethics Board of Ain Shams University.

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The quantitative data with parametric distribution were presented as mean, standard deviations and ranges while the qualitative data were presented as number and percentages. ***Chi-square test*** was used to compare between groups with quantitative data and ***Fisher exact test*** were used instead of chi square test only when the expected count in any cell found less than 5.

The comparison between two independent groups with quantitative data and parametric distribution was done by using ***Independent t-test***. The comparison between more than two independent groups with quantitative data and parametric distribution was done by using ***One Way ANOVA***. ***Spearman correlation coefficients*** were used to assess the correlation between two quantitative parameters in the same group.

RESULTS

This study is a cross sectional study that included 60 patients with systemic lupus erythematosus. They were 5 males (8.3%) and 55 females (91.7%), their ages ranged from 40 to 48.5 years with a mean of 42.95±2.59 years. Their BMI ranged from 18.9 to 64.6 kg/m^2 with a mean of 29.37±6.49. Disease duration ranged from 1 to 240 months with a mean of 71.17 ± 58.62.According to SLEDAI score 16 (26.70%) patients were in remission, 29 (48.30%) patients were in mild activity, 8 (13.30%) patients were in moderate activity and 7 (11.70%) patients were in high activity. Corticosteroids were the most commonly used medications by our SLE patients as it was used by 60 patients, 54 patients (90.0%) received hydroxychloroquine, and 45 patients (75%) received azathioprine, while 2 (3.3%) patients received mofetil. BMD at lumbar spine among the studied SLE patients ranged from 0.71 – 1.47 with a mean of 1.0 ± 0.15 of and at femoral neck ranged from 0.66 1.27 with a mean of 0.9 ± 0.15.

T-score at lumbar spine -4.1 to 2.2 with a mean of -1.4 ± 1.3 and at femoral neck ranged from -2.6 to 2.4 with a mean of -0.8 ± 1.0 9 (table 1). The frequency of osteopenia among the studied SLE

patient was 40.0% and the frequency of osteopenia among the studied SLE patient was 25 % (table 2).

Table (1): Description of BMD measurements at different sites among the studied 60 SLE patients

	BMD		T-score	
	Lumbar spine (L1-L4) (g/cm2)	Femoral Neck (g/cm2)	Lumbar spine (L1-L4)	Femoral neck
Mean± SD	1.0 ± 0.15	0.9 ± 0.15	-1.4 ± 1.3	-0.8 ± 1.0
Range	0.71 - 1.47	0.66 - 1.27	-4.1 - 2.2	-2.6 - 2.4

Table (2): The frequency of low bone mineral density and osteoporosis among the studied 60 SLE patients

		No.	%
Total T-score	Normal	21	35.0%
	Osteopenia	24	40.0%
	Osteoporosis	15	25.0%

The 10-year probability of Major osteoporotic fracture among the studied SLE patients ranged from 1.1 to 5.6 with a mean of 2.36 ± 0.93 and the 10-year probability of Hip fracture ranged from 0 to 2.8 with a mean of 0.41 ± 0.57.

Comparison between mild, moderate, severe disease activity as regards BMD (T-score) at lumbar spine showed that BMD was lower in moderate and severe disease activity than in mild disease activity with a statistically significant difference ($P < 0.05$), whereas BMD, T-score at femoral neck didn't show a statistically significant difference with disease activity ($P > 0.05$) .

There was a statistically significant increase as regard age ($P < 0.05$) in patients with low BMD than patients with normal BMD as measured by T score. Whereas there was statistically insignificant difference ($p > 0.05$) as regards sex, social status, BMI and disease duration, Moreover, there was a statistically near significant increase in the cumulative dose of steroids in patients with low BMD ($P = 0.05$), while there were statistically insignificant as regard other immuno-suppressants and antimalarial drugs difference ($P > 0.05$).

There was a high statistically significant increase in the 10-year probability of major osteoporotic fracture as well as the 10-year probability of hip fracture by ($p<0.01$) in patients with osteoporosis than patients with normal BMD.

Table (3): Correlation between BMD (T score at different sites) and demographic data, medications received by the studied SLE patients

	T-score			
	Neck Femur		Lumbar Spine	
	r	P	R	P
Age (yrs)	-0.135	0.30	-0.308	0.01
Disease duration (month)	-0.103	0.43	-0.249	0.05
Cumulative dose (gm)	-0.337*	0.009	-0.321*	0.012

On correlating BMD (T scores at lumbar spine) with some demographic data we found that there was a significant negative correlation ($P < 0.05$) with age. On correlating BMD (T score at femoral neck) with medication received by the studied SLE patients there was highly significant negative correlation with cumulative dose of steroids ($P < 0.01$) and BMD (T score at lumbar spine) was significant negatively correlated with cumulative dose of steroids ($P < 0.05$) where T score was lower in older patients and larger cumulative doses (table 3).

DISCUSSION

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by periods of exacerbations that can affect any organ system. Organ damage in SLE is the result of the disease itself and/or a consequence of its treatment [(2)].

Osteoporosis is a systemic skeletal disease characterized by decreasing bone mass and microarchitectural deterioration of bone tissue that leads to an increased risk for bone fragility and fracture. Although osteoporosis can be present in any bone, the hip, spine and wrist are most likely to be affected [(16)].

Osteoporosis occurs frequently in patients with systemic lupus erythematosus. Cross-sectional studies have shown a lower bone mineral density in patients with SLE not treated with glucocorticoids compared with healthy control subjects. The risk of fracture appears to be increased in SLE, perhaps nearly five-fold and with a high incidence of fractures occurring in women below 50 years of age [(17)].Many authoritative guidelines advocate the use of BMD and the resultant T scores for monitoring bone loss and guiding treatment because these surrogate markers have good correlations with fracture risk [(18)].

In this cross sectional study, we assessed 60 Egyptian SLE patients ≥ 40 years of age; Aiming to determine frequency of low BMD and osteoporosis among them, we used DXA scan, moreover we used the FRAX tool to estimate the 10-year probability of major osteoporotic (clinical spine, hip, forearm and humerus) and hip fractures. None of the patients gave history of smoking, alcohol intake or pervious fracture and they were not on regular exercise.

Mean values of lumbar spine, femoral neck BMD were 1.0 ± 0.15 and 0.9 ± 0.15 g/cm2, respectively, with mean T-score values at each site of -1.4 ± 1.3 and -0.8 ± 1.0. The mean age diagnosis was 42.95±2.59 years, the mean disease duration was 71.17 ± 58.62 months and the mean BMI was 29.37 ± 6.49. We had 5 male patients (8.3%) and 55 premenopausal female patients (91.7%).

In this study, represented mostly by premenopausal women, the frequency of osteopenia among the studied 60 SLE patients was 40.0% and the frequency of osteoporosis was 25.0%, results that are in consistency with the ones communicated by several previous studies.

Yeap and his coworkers [19] stated that Osteopenia was present in 41.8% of their studied premenopausl patients and 6.1% had osteoporosis [19]. Barbulescu and his coworkers in (2015) demonstrated that prevalence of osteoporosis among studied SLE patients was 36% and osteopenia 40% [20]. ***Franco et al.*** [21] stated that 50 % of patients had osteopenia and 31 % of their patients had osteoporosis Other authors reported prevalence of osteoporosis was varying from 25 to 74 %, these wide variations between different studies would be related to differences in study design, sex, age, ethnicity, disease severity and treatment [6].

Osteoporosis is defined on the basis of bone mineral density because BMD is a strong predictor of future fracture. However, many fractures occur in persons with BMD values that fall above the osteoporosis threshold. Therefore, an algorithm, called FRAX, was then developed to integrate these risk factors with mortality data to estimate the 10-year absolute probability of hip and major osteoporotic (clinical spine, forearm, hip, or humerus) fracture among adults aged 40 and over [15].

Mak and his coworkers [18] demonstrated that the 10-year risk of major fracture risk (%) measure by FRAX among their studied patients was 5.45 ± 6.2 and 10-year risk of hip fracture (%) 1.31 ± 2.3 [18]. while, ***Lee and his coworkers*** [22] demonstrated that the 10-year risk of major fracture risk (%) measure by FRAX among their studied patients was 6.91± 5.92, 10-year risk of hip fracture (%) was 0.62± 0.99 [22].

In view of these outcomes, we found that patients who contributed in our study had relatively lower 10-year risk of major osteoporotic and hip fracture than patients involved in the other two studies, this discrepancy most probably due to our small sample size in comparison to the other two studies, younger age group as we conducted our study on patient younger than 50 years Moreover, we excluded smokers and alcohol consumers and none of our patients gave history of previous bone fracture, all are considerable risk factors when calculating future risk of fracture according to ***Looker et al.*** [15] who also reported that the 10-year probability of major osteoporotic and hip fracture is doubled above the age of 50. The etiology of bone loss in SLE patients has not been well known. Some researchers have proposed that the etiology of bone loss in SLE is multifactorial, and traditional risk factors of osteoporosis (age, postmenopausal status and low body weight or low body mass index) autoimmune inflammation, hormonal factors, and corticosteroid-induced adverse impact may all have been involved in the bone loss in SLE patients [22].So we further analyzed and compared the SLE patients of different groups (normal, osteopenia and osteoporosis), at different sites (lumbar spine and femoral neck) for demographic and clinical variables to find the possible risk factors for osteoporosis in SLE patients. After reviewing all the results we demonstrated that older age was a significant factor associated with low bone mass with ($P < 0.05$). Similar to our results ***Yeap et al.*** [19], ***Carlie et al.*** [23] and ***Cramarossa et al.*** [24] who found that BMD was significantly lower in older patients.

Moreover, in the current study a significant negative correlation was found between T-score at lumbar spine and age of the studied SLE patients (r=-0.308, P= 0.01). Similarly, ***Fonseca et al.*** [25], ***Soto-Santillan et al.*** [26], ***Carlie et al.*** [23], ***Cramarossa et al.*** [24] demonstrated the same correlation between T-score of lumbar spine and age. On the other side, ***Furukawa et al.*** [27], ***El-Hady et al.*** [28], ***Zhu et al.*** [2] and ***Al-Rawi et al.*** [29] found no association between BMD represented by T-score at lumbar spine or femoral neck and age of the studied SLE patients, this is most probably due to different study design and mean age of the studied patients .

In the current study, it was shown that T-score at lumbar spine was statistically significant ($P < 0.05$) lower in patients with moderate and severe disease activity by SLEDAI than in patients with mild disease activity; Similarly, ***Zhang et al.*** [8], ***Souto et al.*** [30], ***Tang et al.*** [31] and ***Zhu et al.*** [2], found that a more active and severe course of disease contributes to bone loss in SLE. Disease flare during follow up was associated with bone loss at lumbar spine. In contrast ***Jacobs et al.*** [32], ***Al-Rawi et al.*** [29] and ***Salman-monte et al.*** [6] did not find a significant relationship between SLE disease activity, measured by the SLEDAI, and low BMD. This probably stems from the low SLEDAI

scores that patients exhibited at the time BMD was performed due to good control of disease activity.

Despite the fact that glucocorticoids are prescribed to SLE patients for long time to improve survival and quality of life, they also promote osteoporosis, especially in sites rich in trabecular bone, as lumbar spine, inducing a high fracture risk [33].In the present study, we found that there was a dose-dependent relationship between glucocorticoids and bone loss at both the femoral neck and lumbar spine the; the higher the cumulative dose of steroid (P = 0.05), the lower bone density. Our results are similar to the results of many other studies ***Jacobs et al.***[32], ***Zhu et al.***[2], ***Carmarossa et al.***[24] ***and Carlie et al.***[23] who have linked the cumulative dose of corticosteroid with low bone density. In contrast, ***El-Hady et al.***[28] and ***Salman-monte et al.***[6] have failed to show an association with glucocorticoids intake and reduced BMD.Additionally, we demonstrated a significant negative correlation between decreased BMD represented by T-score at femoral neck and lumbar spine increased cumulative doses of steroids (r=-0.337, -0.321) (P=0.009,0.012) respectively , which goes in line with ***Yeap et al.***[19], ***Jacobs et al.***[32] and ***Carlie et al.***[23]**.** While, ***El-Hady et al.***[28] and ***Salman-monte et al.***[6] didn't find any relation between bone loss and cumulative dose of steroids this probably due to different disease duration and different treatment strategies between different centers.

On comparing between normal, osteopenic and osteoporotic patients, we found that the higher 10-year probability of major osteoporotic fracture and the 10-year probability of hip fracture, measured by FRAX, were associated with lower values of BMD (P<0.05). ***Mak et al.***[18] have demonstrated that lower hip BMD were independently predictive of higher 10-year probability of major osteoporotic fracture risk only**.**

We tried to find possible risk factors for bone fracture among SLE patients by correlating the 10-year probability of major osteoporotic fracture and hip fracture of studied SLE patients (using FRAX) and some demographic data, medications received by our patients, laboratory data and disease activity by assessed SLEDAI.We found a highly significant positive correlation between patient's age, and cumulative dose of steroids and the 10-year probability of major osteoporotic fracture and hip fracture (r=0.582, 0.469 0.394, 0.344) (P= ,0.000 ., ,0.000,0.002 ,0.007) respectively, this was in accordance with ***Hafez et al.***[34] who demonstrated the same correlations. On the other side the results of ***Mak et al.*** [18] showed that increasing age, cumulative prednisolone dose were independently associated with a higher 10-year probability of major osteoporotic fracture , but 10-year probability of hip fracture associated with older age only .This inconsistency between our results and other studies is most probably due to the limitations that this study had as this was a cross sectional study with a limited sample size that was not sufficient to adjust for more confounders in the multivariate models. We also conducted our study on premenopausal females only. Moreover, FRAX tool model for fracture estimation in which this study applied has limitations. The main limitation of FRAX is the dichotomized risk factors (presence or absence of a parameter) rather than quantifying each risk factor. For example, two previous fractures increase the risk much more than a single previous fracture and increased total consumption (duration and dose) of glucocorticoids, tobacco and alcohol are associated with greater fracture risk. Additionally, while our study design was to exclude patients with a history of clinical or self-reported fracture, patients might have asymptomatic vertebral fractures which led to an underestimation of the fracture risk.

CONCLUSION

There is a high frequency of alterations in BMD among SLE patients; the results were in accordance with other small and large cohort researches, suggesting an increased percentage of low bone mineral density and osteoporosis among SLE patients and a relation to age, disease activity and glucocorticoid treatment.

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