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Research Article

Bone Mineral Density in Patients with Systemic Lupus Erythematosus

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Abstract

Aim: Low Bone Mineral Density (BMD) represents one of Systemic Lupus Erythematosus (SLE) complications, affecting the quality of life in these patients. Evaluation of BMD is done by using DXA (dual X-ray absorptiometry). The aim of this study is to investigate the BMD in SLE patients and to characterize the factors responsible for it.

Material and Methods: The study was done on a group of 21 Caucasian female patients with SLE (SLE group) and 21 Caucasian female apparently healthy, age-matched (Control group). The following parameters were recorded: BMD (T-score at lumbar spine and hip levels), 25(OH) vitamin D, Glomerular Filtration Rate (GFR), SLICC/ACR damage index, age, mean length of SLE evolution, mean Glucocorticoid (GC) dose/day, and the cumulative dose of GC. The data were expressed as mean ± standard deviation. Statistical analyses were performed using the Student's t-test and the Pearson's correlation. Differences were considered statistically significant at the value of $p < 0.05$.

Results: BMD was lower in SLE group than in controls ($p < 0.001$). Reduced BMD was correlated with: SLICC/ACR damage index ($p < 0.001$), mean length of SLE evolution ($p < 0.001$), cumulative dose of GC ($p < 0.001$), 25(OH) vitamin D levels ($p < 0.001$), GFR ($p < 0.001$), and patients age ($p < 0.05$).

Conclusion: Low BMD is a common characteristic in SLE patients. DXA monitoring and initiation of appropriate therapeutic scheme protects the patient from the osteoporosis risks.

Keywords: Bone Mineral Density; Systemic Lupus Erythematosus

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease, characterized by chronic inflammatory process that leads to damages in different organs and systems. Affecting predominantly women of childbearing age, this disease has a chronic evolution with flares and remissions. Due to early diagnosis and effective treatment, the survival of SLE patients has improved in the last years [1]. But although the survival of the SLE patients improved, the risk of comorbidities related to this disease increased. Low bone mineral density (osteopenia and osteoporosis) represents one of these comorbidities. Osteopenia is found in 4% to 74% of SLE patients and osteoporosis in 3% to 48% of them, depending on studies design, age, sex, and ethnicity of the patients [2]. Several factors are involved in osteopenia/osteoporosis appearance in SLE patients: chronic inflammation, SLE damage, prolonged glucocorticoid therapy, inactivity, early menopause, in addition to those risk factors met in the general population. Evaluation of Bone Mineral Density (BMD) is done by using DXA (dual X-ray absorptiometry). Measurement of BMD and expressing as gram per square centimeter and as the number of standard deviation below BMD value in adults in a specific segment of skeleton establishes the diagnosis of osteopenia (T-score between - 1 and - 2.5) or osteoporosis (T-score less than - 2.5) [1]. Chronic pain and fragility fractures represent serious complications of osteoporosis, affecting quality of life and increasing morbidity and mortality of patients in general, and those with SLE, in particular [3]. Osteoporotic fractures associated with SLE were reported differently. In the study performed by Ramsey-Goldman et al., approximately 12.3% of the 702 SLE patients presented at least one fracture during the disease evolution, the most common sites being represented by the leg, foot, arm, spine,

and hip [4]. The aim of this study is to investigate the BMD in SLE patients and to characterize the factors responsible for it.

Material and Methods

The study was done on a group of 21 Caucasian female patients with SLE (SLE group) and 21 Caucasian female apparently healthy, age-matched (Control group). None of the patients and controls had previous fragility fractures. The diagnosis of SLE was established based on 2012 SLICC Classification Criteria for Systemic Lupus Erythematosus [5]. All the patients had disease duration over 2 years. Exclusion criteria were: previous therapy (other than glucocorticoids) which induced osteoporosis, diabetes mellitus, uncontrolled arterial hypertension, dyslipidemia, thyroid and parathyroid dysfunction, Cushing syndrome, current smokers, pregnancy. All the patients gave their informed consent. The study was approved by the Ethics Committee of University of Medicine and Pharmacy "Victor Babeş" Timişoara, Romania. Bone mineral density was determined by DXA (General Electric LUNAR PRODIGY), expressed as T score. The levels of 25(OH) vitamin D (chemiluminescence immunoassay, serum) and glomerular filtration rate (GFR) based on the values of serum, urinary creatinine, and diuresis were determined in both groups.

In SLE group, the following parameters were recorded: SLICC/ACR damage index (https://qxmd.com/calculate/calculator_336/slicc-acr-damage-index), mean length of SLE evolution, mean glucocorticoid (GC) dose/day, and the cumulative dose of GC. The risk of osteoporotic related fracture during the next 10 years was assessed using Fracture Risk Assessment Tool (FRAX) (https://www.sheffield.ac.uk/FRAX). The data were expressed as mean ± standard deviation. Statistical analyses were performed using the Student's t-test and the Pearson's correlation. Differences were considered statistically significant at the value of $p < 0.05$.

Results

The demographic data of SLE patients and controls are presented in the (Table 1).

Parameter	Value (mean ± standard deviation)	
	SLE patients	Controls
Number of patients/controls	21	21
Mean age (years)	43.71 ± 6.8	44.70 ± 8.61
Mean length of SLE evolution (years)	11.61 ± 5.89	-
The drugs used by the SLE patients in the moment of investigation	Glucocorticoids: 21 patients (7.78 ± 2.65 mg/day) Cyclophosphamide: 8 patients (943.75 ± 139.99 mg/month, pulse-therapy) Azathioprine: 13 patients (100 mg/day) Hydroxychloroquine (400 mg/day)	-
Menopause	6 patients (28.57%)	3 controls (14.28%)

Table 1: Demographic data in SLE patients and controls.

All the SLE patients were positive for antinuclear antibodies, anti-DNAds antibodies. The recorded parameters of SLE patients and controls are presented in (Table 2).

Parameter	Value (mean ± standard deviation)		p
	SLE patients	Controls	
Mean age (years)	43.71 ± 6.8	44.70 ± 8.61	> 0.05
Mean length of SLE evolution (years)	11.61 ± 5.89	-	-
SLICC/ACR damage index	7.42 ± 3.41	-	-
GC (mg/day)	7.78 ± 2.65	-	-
GC (cumulative dose, gram)	36.50 ± 26.37	-	-
25 (OH) vitamin D levels (ng/dl)	15.72 ± 5.27	32.35 ± 8.31	< 0.001
GFR (ml/min)	67.14 ± 21.29	77.23 ± 9.45	> 0.05
T-score (lumbar spine)	- 2.56 ± 0.97	- 0.19 ± 1.32	< 0.001
T-score (hip)	- 2.34 ± 0.87	0.005 ± 1.03	< 0.001

Table 2: Laboratory findings in RA patients and controls.

The vitamin D levels in SLE and controls groups are presented in (Table 3).

25 (OH) vitamin D levels	Number of patients	
	SLE group	Controls group
Deficiency	1	0
Insufficiency	20	5
Normal	0	16

Table 3: The values of vitamin D levels.

Based on T-score at lumbar spine and hip, the patients and controls were classified into three classes: normal, osteopenia and osteoporosis (Table 4). None of the SLE patient had normal T-score.

Bone mass density		Number of patients	
		SLE group	Controls group
Normal	Lumbar spine	0	14
	Hip	0	17
Osteopenia	Lumbar spine	11	4
	Hip	13	2
Osteoporosis	Lumbar spine	10	3
	Hip	8	2

Table 4: Bone mass density in studied patients and controls.

Among the SLE patients, the following situations encountered: osteoporosis or osteopenia at two sites (lumbar spine and hip), osteoporosis or osteopenia at one site (lumbar spine or hip), or combination of osteoporosis and osteopenia. The risk of fragility fractures determined based on FRAX score registered: Major Osteoporotic Fracture (MOF) risk 9.67 ± 9.75%, respective hip fracture (HF) 4.2 ± 7.28%. The SLE patients' characteristics related to bone mineral density are presented in (Table 5).

Parameter	Osteopenia	Osteoporosis	p
T-score	- 1.86 ± 0.55	- 3.33 ± 0.71	< 0.05
Mean age (years)	40.36 ± 3.23	47.4 ± 7.91	< 0.05
Mean lenght of SLE evolution (years)	7.63 ± 4.63	16 ± 3.55	< 0.001
SLICC/ACR damage index	5.36 ± 1.80	9.7 ± 3.36	< 0.01
GC (cummulative dose, grams)	18.98 ± 13.60	55.78 ± 23.49	< 0.01
25(OH) vitamin D (ng/ml)	19.54 ± 4.50	11.52 ± 1.36	< 0.001
GRF (ml/min)	80.36 ± 14.66	52.6 ± 17.89	< 0.01
MOF	4,54 ± 1	15.31 ± 11.95	< 0.05
HF	0.88 ± 0.78	7.85 ± 9.42	< 0.05

Table 5: The SLE characteristics related to bone mineral density.

The data showed that the SLE patients with osteoporosis were older, had a prolonged SLE evolution, and high SLICC/ACR damage index. High cumulative dose of GC, reduced levels of 25(OH) vitamin D, and reduced GRF were associated with osteoporosis, too. Correlations between T-score and patient's characteristics are presented in (Table 6).

	Lumbar spine T-score		Hip T-score	
	r	p	r	p
Age	- 0.5266	< 0.05	- 0.4723	< 0.05
Mean length of SLE evolution	- 0.7946	< 0.001	- 0.7357	< 0.001
SLICC/ACR damage index	- 0.8937	< 0.001	- 0.8846	< 0.001
Cumulative dose of GC	- 0.7675	< 0.001	- 0.7303	< 0.001
25(OH) vitamin D	0.9193	< 0.001	0.9118	< 0.001
GRF	0.6840	< 0.001	0.7025	< 0.001

Table 6: Correlations between T score and patients' characteristics.

Discussion

Due to novel therapeutic strategies, the patients with SLE live longer, favoring complications. Bone mineral disease, represented by osteopenia and osteoporosis, represents a serious health problem in SLE patients [6,7]. The bone complications-related SLE has been a concern for the researchers for a long time. The item represented by bone related disease complications is included in damage score for this disease, such as the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index [8]. Osteoporosis, common clinical problem in inflammatory diseases, represents a skeletal disorder which is characterized by reduced bone mass and deterioration of bone microarchitecture, the final results being increased bone fragility and high risk for fragility fractures. In SLE patients, increased bone loss is more frequent than in the general population, several studies confirming that the patients with SLE presented low BMD [1,2]. Previous studies about abnormalities of bone metabolism in SLE showed discordant results [9-11]. Since SLE is a chronic condition, with a prolonged evolution, evolving with flares and remissions, the chronic inflammatory environment (interleukin-1, interleukin-6, TNF-α) contributes to low bone mass. Chronic inflammation generates several damages in different organs and systems. SLICC/ACR damage index evaluates these damages due to SLE activity during the entire period of its evolution (8). The present study revealed that the T-score was significantly reduced at lumbar spine and hip levels in SLE group than in controls group ($p < 0.001$). Strong negative correlations between T-score at lumbar spine, respective hip levels and SLICC/ACR damage index ($p < 0.001$), mean length of SLE evolution ($p < 0.001$), and the patients age ($p < 0.05$) were highlighted.

Sinigaglia et al. identified that the lumbar spine and femoral neck BMD were reduced in 84 premenopausal SLE patients, being correlated with damage index ($p = 0.008$ at lumbar spine level, respective $p = 0.05$ at femoral level). The longer disease evolution was associated with osteoporosis, too (odds ratio 1.2 for each year of SLE, 95% confidence interval 1.07-1.33) [12]. Becker et al. identified in their study that the SLE patients had low BMD, inversely correlated with disease duration, damage score and cumulative glucocorticoid dose. Damage index was the best instrument for the prediction of BMD at both lumbar spine ($r = 0.68$, $p < 0.0001$) and femoral neck ($r = 0.76$, $p < 0.0001$). The authors warned that the reduction of BMD rarely appears during the first 7.5 years of SLE evolution (10). Another study showed that the lower BMD was associated with the higher SLE damage index score ($p = 0.002$ at the hip, $p = 0.02$ at the lumbar spine), longer disease duration ($p = 0.006$ at the hip), older age of the patients ($p = 0.001$) [13]. Studying 30 Asian patients with SLE on long-term corticoids, 30 Asian patients with SLE but not on corticoids, and 60 healthy controls, Tang et al. identified low BMD in both SLE groups compared with controls ($p<0.01$) [14]. Sun et al. found osteopenia in 31.1%, respective osteoporosis in 8.5% of 119 untreated SLE patients [2]. These last two studies revealed that low BMD appeared in SLE patients even in absence of corticoids therapy, reinforcing the hypothesis that chronic inflammation associated with SLE contributes to low BMD. In the study published by Pineau et al. on 205 SLE patients, 18% had osteoporosis, 48.8% had osteopenia and 33.2% had normal BMD. The authors identified that the low BMD was correlated with a higher age at time of BMD investigation ($p = 0.0003$) and a higher damage disease index ($p = 0.0019$) [15]. Chronic damage, assessed by SLICC/ACR damage index increases with the increasing duration of SLE evolution, and this can be associated with osteopenia/osteoporosis [16].

SLE women are prone to early menopause. In the present study, the menopause was found in 28.57% of SLE group versus 14.28% of controls group ($p > 0.05$). Lakshminarayanan et al. demonstrated in their study that in female SLE patients, postmenopausal status is related to ostepenia and osteoporosis [13]. Studying 34 postmenopausal SLE females, Mok et al. demonstrated osteopenia in 33% and osteoporosis in 42% at the lumbar spine level, respective osteopenia in 74% and osteoporosis in 3% at the hip level. Glucocorticosteroids contribute to low BMD appearance by increased apoptosis of osteoblasts and osteocytes, and on the other hand, by inhibition of osteoblasts. Trabecular bone is mainly affected by these processes, which occur rapidly after initiation of corticoid therapy. But glucocorticosteroids down-regulate the expression of osteoprotegerin mRNA and stimulate the Receptor Activator of Nuclear Kappa B Ligand (RANKL). Reduced calcium absorption and increase in calcium excretion contribute to the appearance of glucocorticoid related osteoporosis [1,2,18]. Glucocorticoids doses higher than 7.5 mg/day (Prednison equivalent) are significantly associated with increased risk of low BMD [19]. In the studied SLE group, higher GC cumulative dose was associated with osteoporosis ($p < 0.01$). It was demonstrated an inverse strong correlation between cumulative dose of GC and T-score at lumbar spine and hip levels ($p < 0.001$). Cumulative dose of corticosteroids as a risk factor of osteoporosis/osteopenia in SLE patients was supported by several studies [13,20,21].

Low levels of 25(OH) vitamin D are common among SLE patients, caused by avoiding exposure to the sun or chronic kidney disease. In the present study, 25(OH) vitamin D insufficiency appeared in 20 patients, and its deficiency in one. In contrast, in the controls group, 5 subjects had 25(OH) vitamin D insufficiency, and 16 subjects had normal values of it. The levels of 25(OH) vitamin D have shown a strong negative correlation with T-score at both levels ($p < 0.001$). The studies of Muller et al, Bhattoa et al, Bultink et al., and Jacobs et al. revealed the association between low levels of 25(OH) vitamin D and low BMD in patients with SLE [18,22-25]. Advanced chronic kidney disease secondary to lupus nephritis is associated with low BMD [1]. Chronic renal failure appears to be an important factor for osteoporosis ($p < 0.03$) [21]. In our study, the SLE patients with osteoporosis had GFR less than the patients with osteopenia ($p < 0.01$). Among the drugs used in the treatment of SLE, Hydroxychloroquine requires special attention. This drug, largely used in SLE treatment, appears to protect against low BMD in corticosteroid treated patients with SLE [13]. Both et al. demonstrated that this drug inhibits the formation of multinuclear osteoclasts, and, on the other hand, induces osteoclastic lysosomal membrane permeabilization, leading to decreased bone resorption [26]. Fragility fractures increase morbidity and mortality of SLE patients, affecting the quality of life in these patients [1,2]. In the study of Zhu et al, the incidence of vertebral fracture was 0.94%, and nonvertebral fracture was 1.26% in a cohort of Chinese SLE patients [27]. Bultink reported a prevalence of vertebral fragility fracture of 18-50% in SLE patients, and, interesting, one in three of these patients had normal BMD [18], but SLE patients with fragility fractures had lower BMD than the SLE patients without these fractures [28]. These fractures appear even in pre-menopausal [21]. None of the studied patients presented fragility fractures, but the risk is moderate. The statistical analysis revealed strong correlations between MOF and SLICC/ACR index ($p < 0.001$), patients age ($p < 0.01$), SLE evolution duration ($p < 0.05$), 25(OH) vitamin D ($p < 0.05$), cumulative dose of GC ($p < 0.05$) (these data were not represented in the table). Similar results were reported by Pisani et al. [29].

In order to prevent the occurrence of low BMD in SLE patients, the following recommendations are required: less GC (the lowest possible dose, for the shortest possible time), supplementation with calcium salts and 25(OH) vitamin D, exercise, smoking cessation, and, in selected cases, bisphosphonates [30]. The present study had some limitations. The first limitation was the small sample size, being investigated only 21 SLE patients. Second, it was determined only the serum 25(OH)D. The free bioavailable vitamin D and vitamin D-binding protein were not measured.

Conclusion

Low bone mineral density is a common characteristic in SLE patients, several factors contributing to its appearance: chronic inflammation, SLE damage, prolonged glucocorticoid therapy,

inactivity, early menopause, along with the factors present in the general population. DXA monitoring and initiation of appropriate therapeutic scheme protects the patient from the osteoporosis risks.

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