

Osteoporosis in Systemic Lupus Erythematosus - Correlations with Disease Activity and Organ Damage

ANDREEA BARBULESCU¹, F.A. VREJU², CRISTINA CRIVEANU²,
ANCA ROSU², PAULINA CIUREA²

¹University of Medicine and Pharmacy of Craiova, Pharmacology Department

²University of Medicine and Pharmacy of Craiova, Rheumatology Department

ABSTRACT: Purpose: to assess the incidence of osteoporosis in a cohort of SLE patients and to determine the possible correlations with disease activity, organ damage and glucocorticoid therapy. Material and methods: We analyzed a cohort that included 25 consecutive SLE patients, diagnosed according to ACR revised criteria, and 21 controls, with the same demographic characteristics. We assessed demographic, life style related, clinical, biologic and immunologic data; also, we registered information about the treatment and calculated disease activity and damage scores. Bone mineral density was measured both in lumbar spine and total hip, using dual-energy X-ray absorptiometry. Results: Evaluation of T score profile, both in lumbar spine and total hip, established a percentage of 36 (9) patients with osteoporosis, 40 (10) patients with osteopenia and 24 (6) cases with normal values. Mean T score in lumbar spine was -1.28 ± 1.31 SD and for the total hip -1.21 ± 1.34 SD. Analysis of correlation between T score, both in lumbar spine and total hip, and SLEDAI, established a moderate, negative correlation; for SDI we obtained a moderate correlation, both for lumbar spine and total hip, statistically significant. Conclusions: our results show an increased percentage of osteoporosis among SLE patients and a relation to disease and treatment variables, imposing a periodic evaluation, in order to establish an early diagnosis, the proper therapeutic measures, and to prevent the major consequence, vertebral and non-vertebral fractures.

KEYWORDS: osteoporosis, systemic lupus erythematosus, disease activity, organ damage

Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease, associated with an inflammatory status and multisystemic damage, due to interaction between genetic, immunological, endocrine and environmental factors [1]. Although the incidence of SLE has increased, there has been a significant improvement in the long time survival, inducing a higher incidence of complications and comorbidities [2]. Osteoporosis, a common clinical condition in inflammatory diseases, has an increased prevalence in this group of patients [1, 2, 3].

The etiology of bone loss is multifactorial, including both disease and non-disease related factors. Similar to general population, age, postmenopausal status, low body mass index and white ethnicity represent independent risk factors in these patients [3, 4, 5]. Chronic, systemic inflammation, determines an increased osteoclastic bone resorption and reduced osteoblastic bone formation [3, 6, 7]. Moreover, vitamin D deficiency due to photosensitivity and lack of sun exposure, renal failure or glucocorticoid treatment, contributes to an impaired bone metabolism [8]. Glucocorticoids, extensively used for the treatment of SLE patients can induce bone loss, although, on the other hand, they have a benefic effect on

reducing systemic inflammation. Also, hormonal status, characterized by increased estrogenic and low androgenic state, may negatively influence bone mass [3, 6, 9].

The incidence of osteoporosis in patients with SLE was widely studied and reported by different scientific reports, starting with the nineties until nowadays, in different percentages, ranging from 1.4 to 68%, leading to one of the most important complications, fragility fractures, associated with increased morbidity and mortality [4-6, 10-15]. Therefore, assessing the degree of bone loss becomes extremely important, in order to identify the patients that require therapeutic intervention.

The aim of the study was to assess the incidence of osteoporosis in a cohort of SLE patients and to determine the possible correlations with disease activity, organ damage and glucocorticoid therapy.

Material and methods

We analyzed a cohort that included 25 consecutive SLE patients, diagnosed according to American College of Rheumatology (ACR) revised criteria [16], hospitalized in Rheumatology clinic of Emergency County Hospital Craiova, between June 2014-November 2014, and 21 controls, with the same demographic characteristics. The study was approved by the local ethics committee and

written informed consent was obtained from all patients. We assessed demographic and disease related data from all patients, data presented in Table 1. All of the patients received hydroxychloroquine, immunosuppressive agents and glucocorticoids, in variable doses.

We assessed demographic data (age, sex, body weight, height, body mass index, menstrual status, age at menopause), life style related data (smoking, alcohol intake), clinical, biologic and immunologic data; also, we registered information about the treatment (use of hydroxychloroquine, immunosuppressive agents and glucocorticoids). Disease activity was scored using the Systemic Lupus Erythematosus Disease activity Index (SLEDAI) [17] and European Consensus Lupus Activity Measurement (ECLAM) [18]; a SLEDAI > 8 defines a persistent active disease. Accumulated organ damage was assessed using Systemic Lupus International Collaborating Clinics/ACR damage index (SDI) [19].

Bone mineral density was assessed both in lumbar spine and total hip, using dual-energy X-ray absorptiometry, using a DPX-Alpha (Lunar-General Electric) device. Bone mass was expressed using T score (the number of standard deviations above or below the mean results of young female adults). Osteoporosis was defined, according to WHO criteria, as a T score \leq -2.5 in

lumbar spine or total hip and osteopenia as a T score \leq -1, but $>$ -2.5 [20].

GraphPad Prism 5.5 program was used for statistical analysis. Data were presented as mean \pm standard deviation (mean \pm SD). We compared groups using T-test and calculated Pearson coefficient for establishing correlations. A P value less than 0.05 was considered statistically significant.

Results

The study group included 22 (88%) women and 3 (22%) men, with a mean age of 41.32 ± 11.96 years and a mean disease duration of 7.88 ± 6.07 years (Table 1). Most of the patients were under 50 years old (20; 80%); 3 (12%) of the women were post-menopausal, with a mean duration for menopause of 4.66 years and a mean age for menopause of 44.33 years. Demographic variables of the controls were similar, with a mean age of 40.21 ± 12.91 years.

Regarding disease activity, we registered a mean SLEDAI of 7.56 ± 3.51 , limits 3-20, a mean SDI of 0.84, limits 0-4 and a mean ECLAM 2.92, limits 1-7. For inflammatory markers, we recorded a mean ESR of 33.77 ± 9.22 mm and a mean CRP of 0.78 ± 0.40 mg/dl (Table 1).

Table 1: General characteristics of SLE patients

Parameter	Mean/SD
Age (years)	43.41 ± 11.04
Disease duration (years)	8.364 ± 6.29
Hb (g/dl)	11.27 ± 5.26
Le (no/mm ³)	4109 ± 664.0
Tr (no/mm ³)	161227 ± 36918
Cr (mg/dl)	0.85 ± 0.16
Proteinuria (g/24h)	0.60 ± 1.452
ADNdc (UI/ml)	322.6 ± 241.7
Anti-Sm (UI/ml)	7.65 ± 2.56
C3 (mg/dl)	85.65 ± 21.80
C4 (mg/dl)	28.91 ± 17.93
aCL IgG (GPL/ml)	24.86 ± 16.45
aCL IgM (GPL/ml)	28.91 ± 17.93
ESR (mm/h)	33.77 ± 9.22
CRP (mg/dl)	0.78 ± 0.40
SLEDAI	7.50 ± 0.40
ECLAM	3.09 ± 1.54
GC (N; %)	(25; 100%)
HCQ (N; %)	(25; 100%)
Immunosuppressive agents (N; %)	(16; 64%)

Evaluation of T score profile, both in lumbar spine and total hip, established a percentage of 36 (9) patients with osteoporosis, 40 (10) patients with osteopenia and 24 (6) cases with normal values. 5 patients had values corresponding to osteoporosis for both sites. For control group, osteoporosis was found in 7 (33.3%) patients, osteopenia in 5 (23.80%) and

normal T score in 9 (42.85%) cases (Fig.1). Mean value of T score in lumbar spine (T score L) was -1.28 ± 1.31 SD and for the total hip (T score H) -1.21 ± 1.34 SD. In the control group, we assessed a mean value of 1.09 ± 0.91 SD for T score L and 0.98 ± 1.03 SD for T score H, differences significant statistically in both cases ($p < 0.001$) (Table 2).

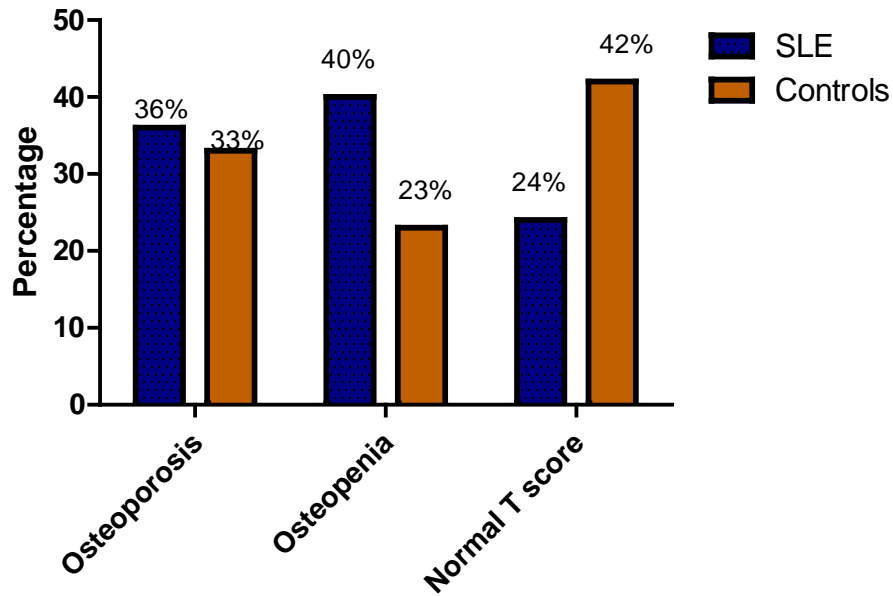


Fig.1: Osteoporosis/osteopenia in SLE/controls

Table 2: T score in SLE and controls

T score	SLE	Controls	p
L	-1.228 ± 1.31	1.09 ± 0.91	< 0.0001
H	-1.21 ± 1.34	0.98 ± 1.03	< 0.0001

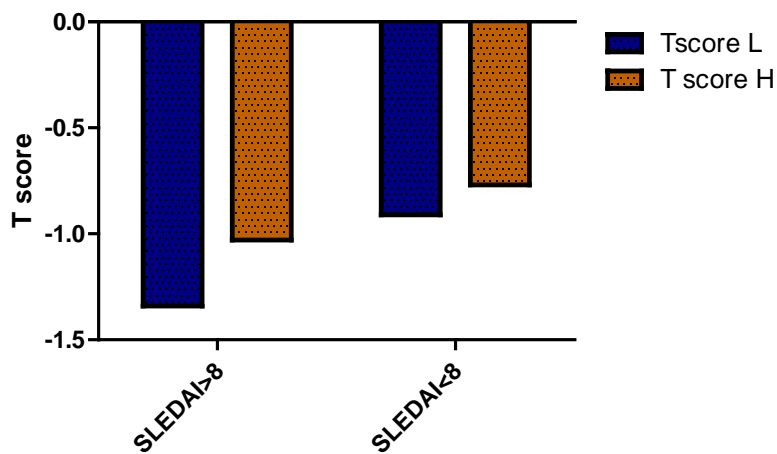


Fig.2: T score L/H related to SLEDAI

Analyzing T score related to SLEDAI, we obtained a mean value in lumbar spine/total hip of $-1.34 \pm 1.68 / -1.03 \pm 1.30$ SD for patients with a persistent active disease (SLEDAI > 8) and $-0.91 \pm 1.23 / -1.03 \pm 1.28$ SD for patients with a SLEDAI < 8, differences not significant statistically ($p=0.153$) (Fig.2). In the SLE group, for the 9 patients with osteoporosis, the mean SLEDAI was 8.22 ± 2.58 versus 7.67 ± 2.21 in the group with osteopenia, $p=0.004$; also, for patients with osteoporosis, mean SLEDAI registered a value of 8.22 ± 2.58 versus 7.67 ± 2.21 in the group with osteopenia, $p=0.004$, the mean

disease duration 9.21 ± 5.91 vs 8.23 ± 4.55 years, $p=0.01$, and the mean age 44.21 ± 10.02 vs 43.09 ± 10.01 years, $p=0.001$.

Analysis of correlation between T score L and SLEDAI, established a moderate, negative correlation of the variables, $r=-0.5068$, $p=0.0097$ (table 3); for ECLAM we registered a Pearson correlation coefficient of -0.21 , not significant statistically ($p=0.23$) and for SDI $r=-0.60$, significant statistically, $p<0.001$. For total hip and SLEDAI the correlation coefficient was -0.4864 , $p=0.013$; for ECLAM $r=-0.28$, $p=0.024$ and for SDI $r=-0.56$, $p<0.001$ (Table 3).

Table 3: Correlations between Tscore L/H, SLEDAI, SDI and GC dose

	TscoreL/ SLEDAI	TscoreH/ SLEDAI	TscoreL/ SDI	TscoreH/ SDI	Tscore L/GC	Tscore H/GC
r	0.506	0.486	-0.60	-0.56	-0.483	-0.483
p	0.009	0.013	<0.001	<0.001	0.014	0.014

We also evaluated whether demographic or other disease related variables are inter-related to T score and we found a negative, moderate correlation between the dose of glucocorticoids both with lumbar T score ($r=-0.483$, $p=0.014$) and total hip T score ($r=-0.463$, $p=0.029$) (Table 3). Disease duration correlated moderate, negative, with T score in lumbar spine ($r=-0.59$, $p=0.001$) and T score H ($r=-0.55$, $p<0.001$).

Discussion

SLE is an autoimmune disease, defined by chronic inflammation and multiple organ damage, that can target any organ or system. Like other chronic, inflammatory disease, SLE is associated with an increased risk of bone loss and osteoporosis, determined by both traditional risk factors and disease related ones.

Assessing bone mineral density and osteoporosis incidence in patients with systemic lupus erythematosus was performed in several studies, from the nineties, starting with the small cohorts of *Dhillon et al* in 1990, *Kalla et al* in 1993 [10, 11], continuing with larger groups until nowadays, and reported different percentages of osteoporosis and osteopenia. The percentage of osteoporosis varies from 1.4% to 68%, suggesting a generalized bone loss in SLE patients. The differences among studies may be due to sex, age, menopausal status, ethnic group, disease duration and activity [4-6, 10-16]. In our cohort, represented mostly by premenopausal women, the prevalence of osteoporosis was 36% and for osteopenia 40% of the cases,

results that are in consistency with the ones communicated by several recent studies [12-15].

We also noticed a difference between the proportion of patients with osteoporosis in lumbar spine (5; 22.7%) and total hip (3; 13.33%) as well as between osteopenia in lumbar site (9; 40.49%) and total hip (2; 9.09%). Other studies reported similar findings, without providing a clear explanation, but related them mostly to bone architecture and effect of glucocorticoid therapy [6, 14, 15, 21, 22]. Glucocorticoids are known to interact with areas that consists in trabecular bone, such as lumbar spine, and induce bone loss, directly inhibiting osteoblasts and bone formation. Moreover, trabecular bone is a direct target for chronic inflammation and disease damage, with an increased risk of osteoporosis and its major complication, fractures [22, 23].

For the studied cohort, disease duration had an impact on bone loss and T score values, both in lumbar spine and total hip, with a moderate, negative correlation of the variables ($r=-0.59$, $p=0.001$ for lumbar site and -0.55 , $p<0.001$ for total hip). *Singilaia et al* [13] found that disease duration is independently associated with osteoporosis in a cohort of 84 premenopausal SLE patients, as well as other studies performed by *Lakshminarayan et al* [24] and *Garcia Carrasco et al.* [6]. Also, disease duration presumes multiple organ damage, represented by SDI, that reflects organ injury, a possible consequence of persistent active disease, and an increased glucocorticoid cumulative dose [9, 25]. 66.66% of the patients with osteoporosis

had a SDI more than 1. A negative, moderate correlation was found between T score L and SDI, $r=-0.60$, statistically significant, $p<0.001$, as well as between T score H and damage index, $r=-0.56$, $p<0.001$. The results are similar to other reports [9, 25, 26] and are explained by the impact of disease and therapy induced negative outcome, included in SDI. Also, Singilaia et al reported correlations between low bone mass and high values of SDI in women with osteoporosis compared with controls; moreover, all patients in this study were receiving variable doses of glucocorticoids, so that the impact of this therapy over the association could not be excluded [13].

Like *Lee et al* [9] and *Zhang et al* [27], analysis of correlation between T score L/H and SLEDAI, established a moderate, negative correlation of the variables; also we have found an impact of persistent active disease (SLEDAI>8), on T score L/H, with differences between the groups, possible also due to an inflammatory status and its impact on the bone. Other studies [10, 28] didn't report a significant association of the variables, these differences being explained by evaluation of disease activity at one point of time and different disease duration for the included patients.

Glucocorticoids, that are prescribed for long time treatment and improve survival, quality of life, also promote osteoporosis, especially in sites rich in trabecular bone, as lumbar spine, inducing a high fracture risk [22, 23]. Several studies, including large or small cohorts, assessed the impact of corticoid therapy on bone loss in patients with SLE. Some of the scientific reports found no association [10, 29, 30], and others found a direct correlation [4, 28, 31]. Our results show a moderate, negative correlation, both for lumbar T score ($r= - 0.483$, $p=0.014$), and total hip T score ($r= -0.463$, $p=0.029$).

Conclusions

Although our study had a relative small number of subjects, the results were in accordance with other small and large cohort researches, suggesting an increased percentage of osteoporosis among SLE patients and a relation to disease and treatment variables. Therefore, evaluation of these patients should also include a screening for osteoporosis, in order to establish an early diagnosis, the proper therapeutic measures, and to prevent the major consequence, vertebral and non-vertebral fractures.

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Corresponding Author: Andreea Barbulescu, University of Medicine and Pharmacy of Craiova, 2 Petru Rareș St., 200349 Craiova, Romania; e-mail: anbarbulescu@yahoo.com