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ORIGINAL ARTICLE

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Bone mineral density, biochemical markers of bone turnover, and hormonal status in men with systemic lupus erythematosus

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Abstract The aim of this study was to evaluate bone mineral density (BMD), biochemical markers of bone turnover, and hormone levels in men with systemic lupus erythematosus (SLE). BMD at L2–L4 lumbar vertebrae (LS), left proximal femur neck, and radius at the ultradistal and mid-33% region was measured by dual-energy X-ray absorptiometry in 23 men with SLE (mean age, disease duration, and cumulative corticosteroid dose were 45.6 years, 11.9 years, and 33.410 g, respectively) and 40 healthy, age- and sex-matched controls. Biochemical markers of bone turnover, parathyroid hormone and 25-hydroxyvitamin D (25-OH-D), testosterone, and dehydroepiandrosterone sulfate (DHEAS) levels were measured. There was no difference in BMD between the SLE and control group. The prevalence of osteoporosis was 17.4% (4 out of 23), found at LS. Biochemical markers of bone turnover were within the reference range. There was a high prevalence of hypovitaminosis D (65.2%), hypotestosteronism (62.5%), and hypodehydroepiandrosterone sulfate (100%). There was no correlation between BMD and duration of disease, corticosteroid doses, SLE Disease Activity Index (SLEDAI), SLE Collaboration Clinics/American College of Rheumatology (SLICC/ARC) damage index, or markers of bone turnover. Bone-specific alkaline phosphatase (BSAP) (r, –0.500; $P = 0.018$) and DHEAS (r, –0.511; $P = 0.013$) correlated with the daily corticosteroid dose. Despite corticosteroid therapy, bone mass in men with SLE was not decreased.

Keywords Systemic lupus erythematosus · Men · Bone mineral density · Biochemical markers of bone turnover · Hormones · Corticosteroids

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Introduction

Systemic lupus erythematosus (SLE) is a rare disease in males [1, 2, 3]. There are many disease-related variables that might play a role in determining the bone mineral density (BMD) in individuals with SLE. Cytokines including interleukin (IL)-6, IL-1, and tumor necrosis factor (TNF)-α are elevated in the serum of patients with SLE [4, 5, 6] and have a direct action on bone, including the stimulation of bone resorption and suppression of bone formation [7]. Other mechanisms resulting in increased susceptibility to bone loss include reduced physical activity associated with arthritis or constitutional symptoms, the deliberate avoidance of sunlight exposure, renal involvement resulting in abnormalities of vitamin D hydroxylation [8], and hypogonadism due to the disease itself or secondary to corticosteroid [9] and cytotoxic therapy [10]. In addition, individuals with early-onset SLE may not attain optimal peak bone mass at skeletal maturity.

BMD, disease-related variables, hormone status, and biochemical markers of bone turnover have been studied in women with SLE [11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27], but data on men with SLE is scarce [16, 21, 26, 28]. The pathogenesis of bone loss is debated and unclear in women with SLE, and even more so in men. Furthermore, BMD, biochemical markers of bone turnover, and hormone status have not been studied together in the same cohort of men with SLE.

The aim of this cross-sectional study was to analyze BMD, biochemical markers of bone turnover, and hormone levels in male SLE patients.

Patients and methods

Twenty-three ambulatory Caucasian men with SLE who fulfilled the updated American College of Rheumatology classification [29] criteria for SLE and a group of 40 healthy, age- and sex-matched controls were studied. Exclusion criteria included liver disease, malignancies, untreated thyroid disease, insulin-dependent diabetes mellitus, functional class III and IV according to the Steinbrocker classification [30], age less than 20 years, the presence of lupus nephritis with serum creatinine concentrations exceeding the upper limit of the normal reference range, any medication known to affect bone metabolism with the exception of vitamin D and/or calcium supplements, and glucocorticoids or other drugs specifically used for the treatment of SLE.

Dual-energy X-ray absorptiometry (DXA) examination was performed using a LUNAR DPX-L densitometer. The following data was recorded: date of birth, body weight, height, history of fracture due to minor trauma, history of medication with an effect on the skeleton, age at date of DXA examination. BMD was measured at L2–L4 lumbar spine (LS), left proximal femur neck (FN), and left forearm radius at the ultradistal (RUD) and 33% shaft (R33%) regions. The ultradistal region consists of a region of interest (ROI) with an axial length of 15 mm centered at a region that is 4% of the ulna length from the end of the ulna. The 33% shaft region consists of a ROI with an axial length of 20 mm centered at a site 33% of the ulna length at the end of the ulna. The coefficient of variation of the technique at our institute was 0.8%, using a phantom measured three times a week during the 2-month period of this cross-sectional study. BMD was expressed as a T score, the number of standard deviations from the mean of young men attaining peak bone mass, using the normative reference values (USA, Caucasian) provided by the manufacturer. Normalcy, osteopenia, and osteoporosis were defined according to the WHO classification [31].

Disease variables collected from patient files included duration of disease calculated from time of diagnosis, history of use of any kind of cytostatics (e.g., methotrexate, cyclophosphamide, and azathioprine), daily corticosteroid dose (mg prednisolone equivalent/day), total cumulative steroid dose (g), the SLE Disease Activity Index (SLEDAI) to assess disease activity [32], and the SLE Collaboration Clinics/American College of Rheumatology (SLICC/ARC) damage index to assess accumulated damage [33]. The cumulative history database included information from routine visits scheduled every 2–3 months and additional visits arranged as dictated by disease activity or complications.

On the basis of their daily steroid dose of prednisolone equivalent, the patients were categorized into three groups: 0, ≤ 7.5 mg/day, or >7.5 mg/day [34]; patients were categorized as such only if they were on the same daily steroid dose for at least 6 months before the DXA examination.

Blood and urine samples were collected on the morning of the DXA examination. Standard methods were used to measure serum calcium, phosphate, glutamic oxaloacetic and pyruvic transaminases, creatinine, total alkaline phosphatase, urine calcium, and creatinine. The following parameters were measured by commercial radioimmunoassay (RIA), enzyme-linked immunoassay (ELISA), or immunoradiometric assay (IRMA): bone-specific alkaline phosphatase (BSAP) (ELISA, ALKPHASE-B Metra Biosystems, CA, USA), osteocalcin (OC) (RIA, OSCAtest BRAHMS Diagnostica, GmbH, Henningsdorf, Germany), serum degradation products of C-terminal telopeptides of type I collagen (serum crosslaps) (ELISA, Serum CrossLaps Osteometer BioTech A/S, Herlev, Denmark), parathyoid hormone (PTH) (IRMA, CoTube, BIO-RAD Diagnostic Group. CA, USA), dehydroepiandrosterone sulfate (DHEAS) (RIA, Ortho-Clinical Diagnostics GmbH, Neckargemünd, Germany), testosterone (RIA, Institute of Isotopes, Budapest, Hungary), and 25-hydroxyvitamin D (25-OH-D) (RIA, Incstar Co, MN, USA). Morning urine was also used to measure type I collagen-specific sequence (urinary crosslaps) using a CrossLaps kit (ELISA) purchased from Osteometer BioTech A/S, Herlev, Denmark.

Descriptive statistics are presented as the mean, median, range, and standard deviation (SD). The t test for independent samples was used to compare the means of the two groups. One-way analysis of variance (ANOVA) was used for group comparison. Pearson's correlation coefficients and t tests examined bivariate relations. A value of $P<0.05$ was considered statistically significant. All analyses were performed using the Statistical Package for Social Sciences (SPSS) statistical software for Windows, version 9.0 (SPSS Inc., IL, USA).

Results

The demographic and basic clinical characteristics of men with SLE ($n=23$) and controls ($n=40$) are shown in Table 1. On comparing the SLE and control group, there were no statistically significant differences in age, body mass index (BMI), daily dietary calcium intake, or BMD at LS, FN, RUD, and R33% (Table 1). The disease-related variables in the men with SLE are shown in Table 2. Two patients had never taken corticosteroids. Eighteen patients were currently receiving corticosteroids. None of the patients was on current therapy with

Table 1 Demographic and basic clinical characteristics of the systemic lupus erythematosus (SLE) and control group

Patient characteristics	SLE ($n=23$)	Control ($n=40$)	P value[c]
Mean age (years)	45.6 ± 12.6	48 ± 10	0.543
Median age (years)[a]	45 (24–69)	51.5 (22–55)	–
Weight (kg)[b]	78.9 (43.6–102)	77.2 (42–96)	0.437
Height (cm)[b]	171.8 (156–187)	171.6 (155–183)	0.869
BMI (kg/m^2)	25.3 ± 4.5	26.1 ± 3.2	0.588
Mean daily dietary calcium intake (g)	509.6 ± 191.2	502.4 ± 193.3	0.912
Median daily dietary calcium intake (g)[a]	500.4 (191.2–877)	448 (296.8–827.6)	–
BMD lumbar spine (gm/cm^2)	1.058 ± 0.166	1.117 ± 0.189	0.329
BMD femur neck (gm/cm^2)	0.947 ± 0.141	0.988 ± 0.154	0.421
BMD forearm-radius ultradistal (gm/cm^2)	0.397 ± 0.065	0.416 ± 0.070	0.400
BMD forearm-radius 33% (gm/cm^2)	0.773 ± 0.070	0.769 ± 0.071	0.854

Values are mean $\pm$ SD unless stated otherwise. BMI, body mass index; BMD, bone mineral density.
[a]Median (range).
[b]Mean (range).
[c]Using the t test for independent samples.

Table 2 Disease-related variables in men with systemic lupus erythematosus (SLE) ($n = 23$)

Disease-related variables	
Mean duration of SLE (years)[a]	11.9 ± 6.9
Median duration of SLE (years)[b]	10 (1–29)
Steroids ever used (*n*)	21 (91%)
Mean daily steroid dose (mg/day)[a]	7.5 ± 6.5
Median daily steroid dose (mg/day)[b]	5 (0–20)
Steroids dose (*n*)	
0 mg/day	5 (21.7%)
≤ 7.5 mg/day	10 (43.5%)
> 7.5 mg/day	8 (34.8%)
Cumulative steroid dose (g)[c]	33.410 (0–144.135)
History of fractures on minor trauma (*n*)	2 (8.6%)
SLEDAI[c]	2.1 (0–15)
Mean SLICC/ARC[a]	3.9 ± 2.1
Median SLICC/ARC[b]	3 (2–9)
Steinbrocker functional class (*n*)	
Class I	21 (91.3%)
Class II	2 (8.7%)
History of use of cytostatics (*n*)	7 (30.4%)

SLEDAI, SLE Disease Activity Index; SLICC/ARC, SLE Collaboration Clinics/American College of Rheumatology.
[a]Mean ± SD.
[b]Median (range).
[c]Mean (range).

drugs affecting bone metabolism. With regards to the history of fracture or minor trauma, one patient had an ankle fracture and another a rib fracture.

According to the WHO criteria, 43.5% and 17.4% of the SLE patients had osteopenia and osteoporosis, respectively, at LS, 56.5% and 4.3% at FN, 26.1% and 13% at RUD, and 21.7% and 4.3% at R33%. On subgrouping the SLE patients according to their daily corticosteroid dose, no statistically significant differences were found with regards to their age, BMI, SLEDAI, SLICC/ARC, daily dietary calcium intake, cumulative steroid dose, or BMD at any of the sites measured. The demographic and clinical characteristics of the SLE patients are presented in Table 3, subgrouped according to daily steroid dose in mg/day (0, ≤ 7.5, > 7.5).

Basic laboratory indices were within the normal range. Mean BSAP, OC, serum crosslaps, urinary crosslaps, PTH, and 25-OH-D levels were within the normal reference range, and mean DHEAS and testosterone levels were lower than the normal reference range (Table 4). Twelve (52.2%) of the patients had vitamin D insufficiency (25-OH-Dlevels of ≥12.5 and ≤ 45 nmol/l) and three (13%) had vitamin D deficiency (25-OH-D levels of < 12.5 nmol/l). PTH was high in three (13%) patients.

In the SLE patients, there was no significant correlation between BMD at any of the sites measured and age, BMI, duration of disease, daily and cumulative corticosteroid dose, daily dietary calcium intake, SLEDAI, SLICC/ARC damage index, or biochemical markers of bone turnover. BMD at any of the sites measured did not correlate with the hormones studied.

BSAP correlated significantly with daily corticosteroid dose (r, -0.500, $P = 0.018$), cumulative corticosteroid dose (r, –0.441, $P = 0.040$), OC (r, 0.565; $P = 0.006$), serum crosslaps (r, 0.512, $P = 0.015$), and urinary crosslaps (r, 0.672, $P = 0.002$). OC correlated with serum crosslaps (r, 0.543, $P = 0.007$) and urinary crosslaps (r, 0.628, $P = 0.004$). Serum crosslaps correlated significantly with urinary crosslaps (r, 0.622, $P = 0.004$). Daily corticosteroid dose correlated significantly with cumulative corticosteroid dose (r, 0.608, $P = 0.002$) and DHEAS (r, –0.511, $P = 0.013$). Cumulative corticosteroid dose correlated significantly with DHEAS (r, –0.486, $P = 0.019$). 25-OH-D correlated significantly with PTH (r, –0.431, $P = 0.040$).

Table 3 Demographic and clinical characteristics of the systemic lupus erythematosus (SLE) patients, grouped according to daily steroid dose (mg/day)

Patient Characteristics	Daily steroid dose (mg/day)		
	0 ($n = 5$)	≤ 7.5 ($n = 10$)	> 7.5 ($n = 8$)
Age, yrs	47.8 ± 16.9	44.3 ± 14.4	45.7 ± 7.8
Age (years)[a]	56 (24–62)	40 (27–69)	45.5 (32–59)
BMI (kg/m^2)	16.2 ± 8.4	10.7 ± 5.1	10.7 ± 7.5
Daily dietary calcium intake (g)[a]	578.8 (377.7–775)	474.6 (191.2–705.4)	510.3 (242–877)
Mean duration of SLE (years)[a]	13 (8–29)	10 (2–21)	8.5 (1–23)
Median duration of SLE (years)[a]	0	5 (5–7.5)	15 (10–20)
Daily steroid dose (mg/day)[a]	0	5 (5–7.5)	15 (10–20)
Cumulative steroid dose (g)[a]	5.850 (0–10.050)	34.220 (4.270–68.400)	34.650 (5.680–137.400)
SLEDAI[a]	0 (0–4)	1.5 (0–6)	0 (0–15)
SLICC/ARC[a]	3 (2–7)	3.5 (2–9)	3.5 (2–8)
BMD lumbar spine (gm/cm^2)	1.071 ± 0.159	1.050 ± 0.118	1.060 ± 0.234
BMD femur neck (gm/cm^2)	0.941 ± 0.169	0.962 ± 0.129	0.932 ± 0.157
BMD forearm-radius ultradistal (gm/cm^2)	0.398 ± 0.062	0.382 ± 0.066	0.415 ± 0.070
BMD forearm-radius 33% (gm/cm^2)	0.742 ± 0.039	0.754 ± 0.086	0.817 ± 0.041

All values are mean ± SD unless indicated otherwise. BMI, body mass index; SLEDAI, SLE Disease Activity Index; SLICC/ARC, SLE Collaboration Clinics/American College of Rheumatology; BMD, bone mineral density.
[a]Median (range).

Table 4 Biochemical markers of bone turnover and hormonal status in men with systemic lupus erythematosus (SLE)

Biochemical markers of bone turnover and hormone levels	SLE ($n=23$)		Reference range
	Mean	Range	
Bone-specific alkaline phosphatase (U/l)	16.38	7.89–33.09	15.0–41.3
Serum degradation products of C-terminal telopeptides of type I collagen (pM)	3497.64	197.45–10900	302–7208
Urine type I collagen-specific sequence (μg/mmol creatinine)	299.18	60.81–1659.37	79–335
Osteocalcin (nmol/l)	1.9	0.6–4	0.67–3.35 (21–30 years) 0.67–2.01 (>30 years)
Parathyroid hormone (pmol/l)	4.5	1.1–12.2	1.2–6.8
25-hydroxyvitamin D (nmol/l)	39.8	6–97.5	23–125
Dehydroepiandrosterone sulfate (mmol/l)	1.9	0.3–4.9	5.4–9.1
Testosterone (nmol/l)	8.9	3.3–17	9–38

Discussion

Osteoporosis in patients with SLE has been widely studied over the last two decades, but most of the series have focused on women [11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27]. Some of these studies have included a limited number of men with SLE [16, 21, 26, 28].

We found no difference in BMD at LS, FN, RUD, or R33% between men with SLE and controls, a finding similar to that of Hansen et al. [21] and Formiga et al. [28]. Formiga et al. [28] found no difference in LS and hip BMD, and Hansen et al. [21] found no significant difference in BMD at LS, FN, distal forearm, or distal 1.5 cm of the third metacarpal bone of the nondominant forearm between the patients and healthy controls. In contrast, in another study [26], LS, FN, and total hip BMD were significantly reduced as compared with healthy controls. Among all the sites measured in our study, LS showed the highest percentage of osteoporosis.

Although no fractures were reported by Formiga et al. [28], we found two patients with one fracture each. As in other studies [21, 26, 28], we also failed to show a correlation between disease activity, disease duration, and BMD. We found no correlation between BMD and daily or cumulative corticosteroid dose, a finding similar to that of Hansen et al. [21] and Formiga et al. [28], although Gilboe et al. [26] did find a significant correlation.

Our laboratory results showed that the mean BSAP, OC, and serum and urinary crosslaps were in the normal reference range. We found no correlation between the biochemical markers of bone turnover or BMD. In a study by Hansen et al. [21], serum OC, alkaline phosphatase, carboxyterminal cross-linked telopeptide of type I procollagen, urinary deoxypyridinoline, and pyridinoline were within the normal range. We found a negative correlation between BSAP and the daily and cumulative corticosteroid dose. Hansen et al. [21] showed no correlation between the markers and BMD or corticosteroid therapy. In our study, none of the markers correlated with disease activity, a finding similar to that of Hansen et al. [21].

Prolonged exposure to extraphysiologic corticosteroid concentrations inhibits synthetic processes in the osteoblast [35], a finding supported by the negative correlation we found between corticosteroid therapy and BSAP.

We found a high prevalence of hypovitaminosis D (65.2%), hypotestosteronism (62.5%), and hypodehydroepiandrosterone sulfate (100%). Others [36, 37, 38, 39, 40, 41, 42] have also reported abnormalities in DHEAS and testosterone levels among SLE patients. The role of 25-OH-D and T in bone metabolism is well documented. Glucocorticoid therapy inhibits testicular secretion of testosterone and adrenal secretion of DHEAS, which is supported by our finding of a negative correlation between corticosteroid therapy and DHEAS, but we failed to find a correlation between corticosteroid therapy and testosterone. The low 25-OH-D levels may be explained by the deliberate avoidance of exposure to the sun and a poor diet.

Although we found a high incidence of hypodehydroepiandrosterone sulfate and hypotestosteronism, we failed to find a correlation with BMD. The lack of correlation between low hormone levels of DHEAS, testosterone, and BMD may be explained by the fact that we found a large range and standard deviation for both DHEAS and testosterone levels and, moreover, the number of patients studied may have fallen below the limit of safe statistical handling.

We also calculated the daily dietary calcium intake in the men with SLE. There was no difference as compared with the controls, but both groups had an intake below the Hungarian average [43] and the mean intake of patients studied by Formiga et al. [28].

Low testosterone, DHEAS, 25-OH-D, dietary calcium intake, and corticosteroid therapy all theoretically point to low bone mass. However, despite the fact that our study includes a higher number of male SLE patients with a higher mean age, SLEDAI, cumulative steroid dose, and longer mean disease duration than earlier studies [21, 28], we did not observe a lower bone mass in our patients that in the controls. Due to the limitation in the numbers of male patients with SLE, future studies will require multicenter participation.

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