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Prevalence of and risk factors for low bone mineral density and vertebral fractures in patients with systemic lupus erythematosus

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ABSTRACT

Objective. To examine the prevalence of and risk factors for low bone mineral density (BMD) and vertebral fractures in patients with systemic lupus erythematosus (SLE).

Methods. We studied 107 SLE patients. Demographic and clinical data were collected, and radiographs of the thoracic and lumbar spine and BMD measurements by dual x-ray absorptiometry were performed. Vertebral deformities were scored according to the method of Genant et al: fractures were defined as a reduction of ≥20% of the vertebral body height. Osteoporosis was defined as a T score less than −2.5 SD and osteopenia as a T score less than −1.0 SD in at least 1 region of measurement.

Results. Osteopenia was present in 39% of the patients and osteoporosis in 4% (93% female; mean age 41.1 years). In multiple regression analysis, low BMD in the spine was associated with a low body mass index (BMI), postmenopausal status, and 25-hydroxyvitamin D deficiency. Low BMD in the hip was associated with low BMI and postmenopausal status. At least 1 vertebral fracture was detected in 20% of the patients. Vertebral fractures were associated with ever use of intravenous methylprednisolone and male sex.

Conclusion. Risk factors for low BMD in SLE patients are low BMI, postmenopausal status, and vitamin D deficiency. While osteoporosis defined as a low T score was found in only 4% of the patients, osteoporotic vertebral fractures were detected in 20%. The high prevalence of low BMD and vertebral fractures implies that more attention must be paid to the prevention and treatment of osteoporosis and fractures in SLE.

INTRODUCTION

Over the last few decades, the survival of patients with systemic lupus erythematosus (SLE) has improved dramatically,[1] and the morbidity pattern has shown a shift toward long-term complications, including osteoporosis. Several studies have demonstrated a high prevalence of low bone mineral density (BMD) in patients with SLE, especially female patients. For example, osteopenia is reported in 25–46% of SLE patients[2-4] and osteoporosis, defined as a T score less than −2.5 SD, is reported in 1–23%.[5-7]

In contrast, little attention is paid to osteoporotic fractures, one of the items of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index for SLE [8]. Studies on fractures in SLE have focused on incident cases of symptomatic vertebral and nonvertebral fractures[2,3,9,10] or on prevalent vertebral deformities, i.e., fractures.[11-17] However, the method used to assess vertebral fractures in 6 of these studies[11,13-17] is not clear, and vertebral fractures were scored using dual x-ray absorptiometry (DXA) images in 1 study.[12] Moreover, in the majority of these studies, only a limited number of patients were evaluated.[11,12,14-17]

The importance of identifying prevalent vertebral fractures in SLE patients is illustrated by the observed association between prevalent vertebral deformities and reduced quality of life in postmenopausal women with osteoporosis[18] as well as increased mortality rates and increased risk of future vertebral and nonvertebral fractures in the general population.[19,20] The aim of the present study was to investigate the prevalence of low BMD and vertebral fractures, as determined by a standardized assessment, and to identify risk factors associated with low BMD and prevalent vertebral fractures in a large population of SLE patients.

PATIENTS AND METHODS

Patients

One hundred seven consecutive patients with a diagnosis of SLE were included in the study. All patients regularly attended the outpatient rheumatology clinic of either the VU University Medical Center, the Jan van Breemen Institute, or the Slotervaart Hospital. These institutes provide primary, secondary, and tertiary care for SLE patients. All patients fulfilled the ACR revised criteria for the classification of SLE[21] and provided informed consent for their participation. The local ethics committee approved the study.

Data collection and clinical measures

All measurements were performed systematically between August 2001 and February 2003. Demographic, patient, and disease characteristics were recorded by interview, self-reported questionnaire, chart review, and a clinical examination that was performed by 1 rheumatologist (IEMB). Data collected at the time of study inclusion were age, disease duration, race, menstrual status, age at menopause, periods of amenorrhea, family history of osteoporosis, ultraviolet (UV) light intolerance, sunshine avoidance, use of sunscreens in the previous year, calculated mean daily dietary calcium intake in the last 3 months, history of (non)vertebral fractures after the age of 25 years, comorbidity, alcohol and tobacco intake, and exercise status. Exercise was determined as the weekly frequency of a minimum of 40 minutes of aerobic exercise performed.

History of corticosteroid use, including intravenous (IV) methylprednisolone use (past and current) and oral corticosteroid use (past use, duration of use in months, maximum dosage ever taken, current use, and actual dosage), was documented. The cumulative corticosteroid dose was not calculated since assessment of the patients in the outpatient clinic takes place every 3 months and some patients had, in the past, been allowed to gradually lower their dosage of oral corticosteroids during the time between 2 visits. As a result, the exact dosage of oral corticosteroids used at every point in time was not available for some patients. For this reason, we preferred to use the available exact data on corticosteroid use only. Past and current use of antirheumatic drugs, calcium supplements, vitamin D supplements, multivitamin supplements, hormone-replacement therapy (HRT), oral contraceptives, antiosteoporosis medications, antiepileptic agents, and anticoagulants were also documented.

Body weight, height, and body mass index (BMI) were assessed. Disease activity was scored using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[22] and the European Consensus Lupus Activity Measure (ECLAM).[23] Accumulated organ damage was assessed with the SLICC/ ACR damage index (DI).[8] A modified DI score was derived as the DI score excluding osteoporotic fractures as a damage item.

Laboratory investigations at the time of study inclusion included routine clinical biochemistry profile, immunologic measures (anti–double-stranded DNA antibodies, complement components, antiphospholipid antibodies), and biochemical and hormonal variables related to mineral metabolism (serum levels of calcium, phosphate, and alkaline phosphatase), thyroid function (thyroid-stimulating hormone), and serum levels of 25-hydroxyvitamin D (25[OH]D). Deficiency of 25(OH)D was defined as a serum level <25 nmoles/liter, based on the laboratory reference value.

BMD measurements

BMD measurements of the hip (total hip and femoral neck) and the lumbar spine (L1–4; anteroposterior view) were performed by a trained technician using the same DXA equipment (model 4500; Hologic, Waltham, MA) in all patients, and the results were expressed in grams per square centimeter. Hip measurement was not performed in 3 patients because of bilateral hip replacements. The BMD values were compared with lumbar spine data from a large reference population, as supplied by the manufacturer (Hologic) and National Health and Nutrition Examination Survey reference database for the hip, including data for T score and Z score estimations.

Assessment of vertebral deformities

Lateral radiographs of the thoracic and lumbar spine (T5–L4) were performed in the same radiology department by a trained operator and according to a standardized protocol. All radiographs were of good quality, with good visibility and reliable identification of all vertebrae. Spine radiographs were scored by 2 experienced observers (WFL and BACD) using a standardized semiquantitative method described by Genant et al.[24] This method grades vertebrae on a scale of 0–3, where grade 0 = normal, grade 1 = 20–25% reduction in height, grade 2 = >25–40% reduction in height, and grade 3 >40% reduction in height. For the anterior and middle heights, the posterior height of the same vertebra was used as a reference. A vertebral fracture was defined as a reduction of at least 20% of the vertebral body height. For quality assurance, blinded scoring was done after 7 months, involving 30 SLE patients, 60% of whom had at least 1 vertebral fracture, and 10 controls, 50% of whom had at least 1 vertebral fracture. The kappa value for whether an SLE patient was classified as having any vertebral fracture was 0.62.

Statistical analysis

Variables possibly associated with a decreased BMD or the presence of vertebral fractures were examined first by univariate tests and subsequently by multiple regression analysis. The following variables were examined in relationship to BMD by univariate analyses: age, sex, race, menopause status, BMI, disease duration,

disease activity, modified DI score, exercise, use of sunscreens, UV light intolerance, dietary calcium intake, previous nonvertebral fractures, creatinine clearance, 25(OH)D deficiency, ever use of corticosteroids and IV methylprednisolone, duration of corticosteroid use, current use of corticosteroids and IV methylprednisolone, and past and current use of anticoagulants. Univariate analyses of variables possibly associated with vertebral fractures included BMD of the lumbar spine and hip as a variable.

To determine which factors were significantly associated with low BMD or with vertebral fractures, the demographic, clinical, and treatment variables showing $P < 0.2$ in the univariate analyses and variables with supposed clinical relevance were entered into the respective multiple regression analyses. The multiple regression models were refined by tentatively adding to the (almost) final model single variables that were not initially included in the model, so as to check once more whether these variables could indeed be missed. Confidence intervals for percentages were calculated with the Wilson method. A P value less than or equal to 0.05 (2-sided) was considered statistically significant. The software used was SPSS for Windows, version 11.0 (SPSS, Chicago, IL).

RESULTS

Clinical, demographic, and treatment variables.

The clinical and demographic characteristics of the 107 SLE patients included in the study are shown in Table 1. The majority of the patients were premenopausal, female, and Caucasian. At the time of study inclusion, most patients had mild disease activity and little organ damage. Decreased renal function was found in only a small percentage of the patients. 25(OH)D deficiency was detected in 8% of the patients. A history of at least 1 nonvertebral fracture following the diagnosis of lupus was present in 11% of the patients. The majority of patients had taken corticosteroids and hydroxychloroquine. Bisphosphonates and HRT were taken by a small number of patients.

Findings of BMD measurements.

The results of the BMD measurements are shown in Table 2. The frequency of osteoporosis (T score less than −2.5 SD at the lumbar spine [L1–L4] and/or at the total hip) was 4.0%. The frequency of osteopenia (T score less than −1.0 SD at the lumbar spine [L1–L4] and/or at the total hip) was 39%.

Table 1. Demographic, clinical and treatment variables in the study patients

Variable	All patients (n = 107)
Demographic variables	
Female sex, %	93
Premenopausal, %	72
Caucasian race, %	79
Age, mean ± SD years	41 ± 13
Body mass index, mean ± SD kg/m2	25 ± 6
Current smoker, %	22
Exercise ≥ 3 times weekly, %	29
Daily dietary calcium intake, mean ± SD mg	775 ± 317
Clinical variables	
Disease duration, mean ± SD years	6,9 ± 6,7
SLEDAI, mean ± SD	4,9 ± 4,0
ECLAM, mean ± SD	3,1 ± 1,6
SLICC/ACR damage index, mean ± SD	1,4 ± 1,9
SLICC/ACR damage index modified, mean ± SD	1,3 ± 1,9
Erythrocyte sedimentation rate, mean ± SD mm/hour	26 ± 25
C-reactive protein, mean ± SD mg/l	11 ± 16
Creatinine clearance < 70 ml/min, %	18
Ever had lupus nephritis, %	21
25-hydroxyvitamin D deficiency, %	8
Ultraviolet light intolerance, %	59
Use of sunscreen, %	61
Previous nonvertebral fracture, %	11
Previous symptomatic vertebral fracture, %	2
Therapy variables	
Oral corticosteroids	
Ever use, %	81
Current use, %	54
Treatment duration in ever users, mean ± SD months	62 ± 69
Actual prednison dosage, mean ± SD mg/day	
All patients	7 ± 11
Current users only	13 ± 12
Ever use of other medications, %	
Methylprednisolone	17
Hydroxychloroquine	87
Cyclophosphamide	11
Methotrexate	13
Phenprocoumon (slow-acting coumarin derivative)	4
Hormone-replacement therapy	11
Bisphosphonates	22
Current use of other medications, %	
Methotrexate	3
Hormone-replacement therapy	5
Bisphosphonates	16
Calcium supplements	51
Vitamin D supplements	33

SLEDAI = Systemic Lupus Erythematosus Disease Activity Index (range 0-105); ECLAM = European Consensus Lupus Activity Measure (range 0-10); SLICC/ACR = Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index (modified damage index excludes osteoporotic fractures as a damage item)

Table 2. BMD variables and assessment of vertebral deformities*

Variable	All study patients (n = 107)
BMD, mean ± SD g/cm2	
Spine L1-L4	1.02 ± 0.15
Total hip	0.91 ± 0.13
T score, mean ± SD	
Spine L1-L4	-0.23 ± 1.32
Total hip	-0.27 ± 1.06
Z score, mean ± SD	
Spine L1-L4	0.24 ± 1.35
Total hip	0.49 ± 1.11
Osteopenia, %	
Lumbar spine and/or total hip	39
Lumbar spine	35
Total hip	29
Osteoporosis, %	
Lumbar spine and/or total hip	4
Lumbar spine	3
Total hip	2
Vertebral deformities in 90 SLE patients, %	
At least 1 vertebral deformity	20
At least 2 vertebral deformities	7
Severity of 26 vertebral deformities in 90 SLE patients, %	
Grade 1 (20-25% reduction of height)	73
Grade 2 (25-40% reduction of height)	23
Grade 3 (>40% reduction of height)	4

* Osteopenia is defined as a T score less than -1.0 SD. Osteoporosis is defined as a T score less than -2.5 SD in at least one region of measurement. Vertebral deformities are defined as at least a grade 1 deformity (≥ 20% reduction of vertebral body height) according to the method of Genant et al.[24] BMD = bone mineral density. SLE = systemic lupus erythematosus.

Variables associated with BMD.

Univariate analyses. There was a significant association between low BMI and low BMD at the spine (B = 0.0052, P = 0.045) and at the total hip (B = 0.0079, P = 0.001). Postmenopausal status was significantly associated with low BMD at the spine (B = −0.076, P = 0.017), but not at the hip. There was also a significant negative association between the creatinine clearance and low BMD at the hip (B = 0.0011, P = 0.027), but not at the spine. Moreover, ever use of phenprocoumon (a slow-acting coumarin derivative) was significantly associated with low BMD at the hip (B = −0.19, P = 0.01), but not at the spine. BMD at the spine and at the total hip were not associated with age, race, disease duration, disease activity, or measures of corticosteroid exposure (past and current IV methylprednisolone use, past use of oral corticosteroids, duration of oral corticosteroid use, maximum dosage of oral corticosteroid ever taken, current use of oral corticosteroids, and actual oral corticosteroid dosage).

Multiple regression analyses. In a multiple regression analysis of the relationship between menstrual status, BMI, age, and serum 25(OH)D deficiency as independent variables and BMD at the spine as the dependent variable, postmenopausal status (P = 0.001), low BMI (P = 0.025), and serum 25(OH)D deficiency (P = 0.047) were significantly associated with low BMD at the spine. In a multiple regression analysis of the relationship between menstrual status, sex, and BMI as independent variables and BMD at the hip as the dependent variable, low BMI (P = 0.0001) and postmenopausal status (P = 0.037) were significantly associated with low BMD at the hip (Table 3). None of the other variables investigated demonstrated a significant contribution to the model for spine or hip BMD. The final models explained 40% of the variation for spine BMD and 43% of the variation for hip BMD.

Vertebral deformities.

Lateral spine radiographs were available in 90 patients. Osteopenia was present in 39% of these patients and osteoporosis in 3%. The results of the assessment of vertebral deformities are shown in Table 2. The total number of vertebral fractures, defined according to Genant et al as a reduction of the vertebral body height by at least 20%, was 26. Of all vertebral fractures, 89% were located in the thoracic spine and 11% in the lumbar region. At least 1 vertebral fracture was observed in 18 patients (20%; 95% confidence interval 13–29) and at least 2 vertebral fractures in 6 patients (7%; 95% confidence interval 3–14). Twentyseven percent of vertebral fractures were grade 2 (at least 25% reduction of vertebral body height) or higher.

Variables associated with vertebral deformities.

Univariate analyses. There was a significant association between male sex (B = 0.47, P = 0.001) and age (B = 0.0075, P = 0.024) and fractures in the thoracic and/or lumbar spine. Furthermore, there was a trend toward previous nonvertebral fractures (B = 0.27, P = 0.054), ever use of IV methylprednisolone (B = 0.21, P = 0.054), and non-Caucasian race (B = −0.19, P = 0.058).

Multivariate analyses. In a multivariate analysis of the relationship between vertebral fractures as the dependent variable and sex, age, race, modified DI, previous nonvertebral factures, and ever use of IV methylprednisolone as the independent variables, ever use of IV methylprednisolone (P = 0.01) and male sex (P = 0.002) were significantly associated with fractures in the thoracic and/or lumbar spine (Table 3).

Table 3.
Multiple regression analyses of BMD at the lumbar spine, BMD at the total hip, and vertebral deformities (dependent variables) and demographic, clinical, and treatment variables (independent variables)*

Variable	B	SE	*p* value
BMD at the lumbar spine in 107 SLE patients			
Postmenopause	-0.14	0.04	<0.01
Body mass index	0.0058	0.0030	0.025
Age	0.0021	0.001	0.140
25-hydroxyvitamin D deficiency	-0.10	0.051	0.047
BMD at the total hip in 107 SLE patients			
Postmenopause	-0.060	0.029	0.037
Male sex	0.088	0.048	0.07
Body mass index	0.0092	0.0020	<0.0001
Vertebral deformities in 90 SLE patients			
Ever use of IV methylprednisolone	0.28	0.105	0.01
Nonvertebral fractures	0.19	0.141	0.18
SLICC/ACR damage index modified	-0.013	0.024	0.61
Male sex	0.47	0.143	0.002
Age	0.0039	0.0040	0.29
Noncaucasian	-0.13	0.099	0.21

* BMD = bone mineral density; SLE = systemic lupus erythematosus; IV = intravenous; SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology; B = regression coefficient (when considered in the multiple regression model); SE = standard error of B.

Discussion

This is the first study on the estimation of prevalent vertebral fractures in a large group of SLE patients, using a standardized semiquantitative method of scoring vertebral deformities. Associations between clinical data and low BMD and vertebral fractures were also evaluated in this large group of SLE patients. The main conclusion from our study is that low BMD and vertebral fractures are observed frequently in SLE patients, which emphasizes that osteoporosis is a common feature in SLE. In addition, we found a significant association between the prevalence of vertebral fractures and ever use of methylprednisolone and male sex.

The frequency of osteopenia found in our population (39%) is consistent with previous studies showing osteopenia in 25–46% of SLE patients.[2-4] The prevalence of osteoporosis in our patients (4%) was in the lower range seen in previous studies of patients with SLE (1.4–23%).[5-7] The association between postmenopausal status and low BMD found in 2 previous studies in female patients with SLE[5,25] and the association between low BMI and low BMD demonstrated in other studies in SLE patients[5,6,26-28] were confirmed in the present study.

Deficiency of serum 25(OH)D was significantly associated with low BMD in the lumbar spine in our patients. Low serum levels of 25(OH)D in SLE patients have been previously described and are usually ascribed to conscious avoidance of exposure to the sun and/or the use of sunscreens by these patients.[29-32]

Surprisingly, a relationship between corticosteroid use and low BMD could not be demonstrated in our study. This observation is supported by various studies in SLE patients[12-15,28-30,33-35] but is in conflict with other studies in SLE patients in which an association between corticosteroid use and low BMD in the lumbar spine and/or the hip was demonstrated.[2,3,5-7,11,16,17,25,26] The reasons for this discrepancy are unclear but may be related to differences between patient populations in, for example, size, mean age, disease duration, and menstrual status, as well as differences between centers in treatment strategies for osteoporosis, use of corticosteroids, and differences in assessments of corticosteroid use.

Subanalyses of variables associated with low BMD at the lumbar spine and at the hip in patients who had never been treated with bisphosphonates and/or HRT (n = 77) confirmed the importance of low BMI and postmenopausal status as major risk factors for low BMD at lumbar spine and at the hip, both in univariate and multiple regression analyses (data not shown). In these subanalyses, 25(OH)D deficiency was not significantly associated with low BMD, a finding that might be explained by the

small number of patients with 25(OH)D deficiency in the subgroup.

The most striking finding of the present study was the high prevalence of vertebral fractures in our patients (20%), who had a mean age of 41 years, compared with a prevalence of 12% in the general population of Europe ages 65–69 years.[36] One would expect a lower prevalence of vertebral fractures in a younger population.[36]

Only a few studies on fractures in SLE have been published, and these were focused on incident symptomatic vertebral and nonvertebral fractures. In 4 studies, symptomatic vertebral and nonvertebral fractures occurring since the onset of lupus were documented in 9–16.5% of patients.[2,3,5,9] However, studies focusing on symptomatic fractures have a disadvantage in that only one-third of all vertebral fractures come to clinical attention.[37] In the present study, only 2 of 18 patients with 1 or more prevalent vertebral fractures had a documented previous symptomatic vertebral fracture, which illustrates the possibility of underestimating vertebral fractures in patients with SLE if only symptomatic fractures are considered in the scoring.

The association between ever use of IV methylprednisolone and the prevalence of vertebral fractures in this study is consistent with 2 studies documenting an association between corticosteroid use and symptomatic fractures in SLE.[9,10] The association between male sex and prevalent vertebral fractures in our study is not surprising, since in the general population, the prevalence of vertebral fractures at ages younger than 65 years is higher in men than in women.[36]

A subanalysis of factors associated with grade 1 vertebral fractures (according to the method of Genant et al) demonstrated the same significant association between ever use of IV methylprednisolone and prevalent vertebral fractures, both in univariate and multiple regression analyses (data not shown). These results demonstrate that ever use of IV methylprednisolone is also a strong risk factor for prevalent vertebral fractures after the 26% more severe fractures were excluded from the analyses. The subanalysis of factors associated with Genant grade 1 vertebral fractures did not show an association with male sex (data not shown). This finding can be explained by the small number of male patients in the study and the fact that 3 of the 5 male patients with at least 1 vertebral fracture had a fracture that was a Genant grade 2 or more.

Limitations of the present study are the racial background of the study population and the method used to assess corticosteroid use. As a consequence of the rather high percentage of Caucasians in the study population (79%), the associations found

in the present study may not be generalized to lupus cohorts with a significantly different racial background. Second, since the cumulative oral corticosteroid dose was not calculated, associations between the cumulative corticosteroid dose and BMD and prevalent vertebral fractures could not be assessed. However, all other measures of oral corticosteroid use we assessed were not associated with BMD or vertebral fractures.

The results of this study suggest that attention must be paid to the prevention and treatment of osteoporosis and fractures as an important disease complication. Prevention strategies directed toward SLE patients who are at risk of osteoporosis include advice for maintaining a normal body weight and performing weight-bearing physical activity, calcium and vitamin D supplementation in cases of deficiency, and treatment with appropriate antiosteoporosis medication in cases of osteoporosis and/or a vertebral fracture. When considering osteoporosis, osteopenia in combination with corticosteroid use and/or the prevalence of 1 or more vertebral fractures as a reason for treatment with antiosteoporosis drugs, 40% of the patients in our study should have been treated with antiosteoporosis drugs. At the time of the study, only 16% of the patients were taking bisphosphonates and 5% were taking HRT.

The high prevalence of vertebral fractures in our study indicates that the assessment of fracture risk in SLE patients should include assessment of vertebral fractures, since these are often asymptomatic and are clinically important in terms of morbidity, mortality, and future fracture risk. Therefore, we recommend that in the assessment of osteoporosis and future fracture risk in SLE patients, spine radiographs (analyzed using a standardized method for scoring vertebral deformities) and measurements of spine and hip BMD be performed.

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