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Original Article

Assessment of the risk of low bone mineral density in premenopausal Japanese female patients with systemic lupus erythematosus

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ABSTRACT

Background: The aim of this study was to assess the relationships between clinical parameters and bone mineral density (BMD) in Japanese female patients with systemic lupus erythematosus (SLE).

Methods: A total of female 136 SLE patients without menopause were retrospectively assessed to identify associations between age, disease duration, body mass index (BMI), glucocorticoid usage and disease activity and BMD based on the treatment with or without bisphosphonate. There were 71 patients treated with bisphosphonate (bisphosphonate group) and 65 patients without (non-bisphosphonate group). We evaluated the impact of age, disease duration, BMI, serologic SLE markers, glucocorticoid use on BMD of the anterior-posterior (AP) and lateral lumbar spine, total hip and femoral neck using univariate and multivariate linear regression analyses of both bisphosphonate and non-bisphosphonate groups.

Results: Multivariate linear regression analyses showed that in non-bisphosphonate group disease duration was negatively associated with BMD of AP spine and femoral neck, whereas in bisphosphonate group these negative associations were not present. However, multivariate linear regression analyses showed a significant relationship between BMI and BMD of the AP spine, femoral neck and total hip, regardless of bisphosphonate treatment.

Conclusions: Bisphosphonate treatment eliminated the negative relationships between disease duration and the BMD of the spine and hip. AP spine and hip BMD in patients with SLE depend on BMI, regardless of bisphosphonate use. SLE serologic markers and glucocorticoid use were not negatively associated with generalized bone loss. SLE patients with low BMI have a high risk of generalized bone loss, and should be assessed and treated to prevent osteoporosis even before menopause.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by diffuse inflammation that causes damage to multiple organ systems simultaneously or sequentially.[1] SLE primarily affects women of childbearing age and older. Disease control is necessary to prevent irreversible organ damage.[2] The primary drugs used to treat SLE include glucocorticoids and immunosuppressants. Long-term glucocorticoid treatment is required to control SLE and can cause steroid-induced osteoporosis, even in young women.[3–5] Osteoporosis is a common and important comorbidity associated with collagen diseases such as rheumatoid arthritis and SLE. A previous study evaluated the prevalence and predictors of low bone mineral density (BMD) in menopausal women with rheumatoid arthritis.[6] Like as rheumatoid arthritis, SLE patients have a high risk of osteoporosis and fragility fractures because of various factors, such as glucocorticoid use, biochemical abnormalities and restricted physical activity.[7,8] Previous studies have reported that premenopausal SLE patients have increased rates of low vitamin D and low BMD compared with healthy patients.[9,10]

BMD calculated with dual-energy X-ray absorptiometry is currently the gold-standard imaging method for the assessment of osteoporosis and fracture risk.

There is a strong association between BMD and bone strength, but asymptomatic vertebral fractures can occur in SLE patients without apparent bone loss.[11] Some studies on osteoporosis in SLE patients have found significant glucocorticoid-induced bone loss.[12–15] However, others have failed to find this association.[16,17] The reason for the increased bone fragility of SLE patients is not fully understood.

The aims of this study were to identify associations between BMD

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(lumbar spine, hip) and the clinical parameters of SLE, such as disease duration, glucocorticoid treatment, disease activity factors and body mass index (BMI) and to find risk factors for low BMD in Japanese premenopausal patients with SLE. We hypothesized that the spine and hip BMD are associated with disease duration and BMI in premenopausal female patients. We also hypothesized that lateral lumbar BMD measurements can allow earlier detection of the bone loss compared with AP spine and hip BMD measurements.

2. Materials and methods

2.1. Patients

This cross-sectional, retrospective study was approved by the Institutional Review Board at our institute. All patients provided written informed consent. The study population included 136 Japanese premenopausal women with SLE. All patients fulfilled the American College of Rheumatology revised criteria for the diagnosis of SLE[18] We included patients regardless of their prior use of bisphosphonates. Patients were enrolled at our institution from September 2013 through August 2016. We excluded patients with parathyroid disease, chronic severe renal dysfunction and malabsorption disease, as well as patients who had undergone parathyroid hormone treatment. We also excluded patients who had avascular necrosis of the hip and vertebral fractures caused by high-velocity injuries.

2.2. Assessment of demographics and SLE disease activity

The following demographic data were recorded: age, disease duration, BMI, current glucocorticoid use, previous history of high-dose glucocorticoid treatment (more than 1 mg/kg) and the use of drugs for osteoporosis treatment. We assessed SLE disease activity by measuring SLE serologic markers: C-reactive protein (CRP), complement 3 (C3), complement 4 (C4) and anti-double stranded (ds) DNA antibody. We also assessed renal dysfunction by measuring creatinine (Cr). All assessments were performed at the same time as BMD measurement.

2.3. Assessment of BMD and radiographs of thoracic and lumbar spine

We measured BMD (g/cm^2) on the AP and lateral views of the lumbar spine (vertebrae L2–4) and left hip (total hip and femoral neck) with dual-energy X-ray absorptiometry (Discovery DXA system; Hologic, Waltham, MA, USA). We also assessed the relationship between lateral lumbar spine BMD and clinical parameters in these patients. Lateral lumbar spine BMD measurements can be made with acceptable precision[19] and have been found to be more sensitive than anterior-posterior (AP) lumbar BMD measurements in detecting bone loss in postmenopausal women.[20] All procedures were performed according to the manufacturer's standardized protocols. All BMD results are expressed as absolute values (g/cm^2) and as the number of standard deviations (SD) above or below the mean result of young adults (T score). Thoracolumbar radiographs were obtained in all patients to detect vertebral fractures, including both painful vertebral fractures and asymptomatic morphologic vertebral fractures.

2.4. Statistical analysis

Comparisons between the bisphosphonate and non-bisphosphonate groups were performed with the Mann–Whitney *U* test. To identify associations between BMD (absolute value) and clinical parameters such as age, disease duration, BMI, C3, C4, anti-ds DNA antibody, Cr, current glucocorticoid dose and high-dose glucocorticoid treatment history, we conducted univariate and multivariate linear regression analyses in the bisphosphonate and non-bisphosphonate groups. We performed stepwise multivariate linear regression analyses to evaluate the significance of the relationship between the clinical parameters and BMD of the AP lumbar spine, lateral lumbar spine, total hip and femoral neck to assess which variables influenced clinical outcome. Those variables were analyzed as independent factors with stepwise linear regression. All statistical tests were two-sided; *p*-values less than 0.05 were considered statistically significant. All analyses were performed with JMP version 12 (SAS, Cary, NC, USA).

Table 1
Clinical characteristics of patient cohort, shown as number (percentage) and mean (standard deviation).

Patient Characteristics	Values
Mean age (years)	38.8 (9.6)
Mean disease duration (years)	12.9 (8.7)
Body Mass Index	21.8 (4.3)
Bone mineral Density (g/cm^2)	
Lumbar spine AP	0.89 (0.12)
T score	−1.13 (1.04)
Lumbar spine lateral	0.63 (0.09)
T score	−2.15 (1.35)
Total Hip	0.77 (0.12)
T score	−1.06 (1.12)
Femoral Neck	0.67 (0.12)
T score	−1.12 (1.03)
SLE serological markers	
C3 (mg/dl)	85.7 (23.7)
C4 (mg/dl)	17.2 (7.5)
dsDNA	16.9 (27.8)
CRP (mg/dl)	0.23 (0.38)
Creatinine (mg/dl)	0.65 (0.21)
Current dose of glucocorticoid (mg)	8.7 (3.2)
High dose glucocorticoid use	85 (63.3)
Previous fracture	14 (10.3)

3. Results

3.1. Patient demographics

The study population included 136 premenopausal female patients. The clinical characteristics of these patients, including age, disease duration, BMI, BMD, SLE serologic markers, current glucocorticoid dose, previous history of high-dose glucocorticoid treatment and previous fractures, are shown in Table 1. Lateral lumbar spine BMD was assessed in 84 patients. Patients were divided into two groups on the basis of treatment with (n = 71; bisphosphonate group) or without bisphosphonates (n = 65; non-bisphosphonate group). The AP lumbar spine BMD was significantly higher in the group not treated with bisphosphonates (Table 2). Ten patients in the bisphosphonate group and four patients in the non-bisphosphonate group had previous vertebral fractures. The bisphosphonate group included patients with a higher risk of fragility fractures compared with the non-bisphosphonate group. In both groups, both the absolute BMD value and the T score of the lateral lumbar spine were much lower than those of the AP spine, total hip and femoral neck. Measurement of lateral spine BMD might allow earlier detection of bone loss than AP spine and hip BMD measurements in patients with SLE. The mean age of patients in this study was 38.8 years. This is younger than patients with postmenopausal osteoporosis, so degenerative changes in the lumbar spine were not severe and did not affect lumbar spine BMD. These results suggest that, unlike patients with postmenopausal osteoporosis, BMD measurements of the lumbar spine in SLE patients would adequately reflect generalized bone loss.

3.2. Associations between BMD and clinical variables in SLE patients

Univariate linear regression analyses of the non-bisphosphonate group showed that age was negatively associated with femoral neck BMD and disease duration was negatively associated with BMD of the AP lumbar spine, lateral lumbar spine, total hip and femoral neck. BMI was positively associated with AP spine, total hip and femoral neck