Bone mineral density in systemic lupus erythematosus: comparison with rheumatoid arthritis and healthy controls

Inge-Margrethe Gilboe, Tore K Kvien, Glenn Haugeberg, Gunnar Husby

Abstract

Objectives—To examine bone mineral density (BMD) frequency of osteoporosis and reduced bone mass in systemic lupus erythematosus (SLE), and compare the data of the SLE patients with matched rheumatoid arthritis (RA) patients and healthy controls. Secondly, to study possible correlations between BMD, demographic and disease variables in the SLE patients.

Methods—Measures of BMD assessed by dual energy x ray absorptiometry were obtained from 75 SLE patients aged ≤ 70 years, 75 RA patients matched for age, sex and disease duration, and from 75 healthy controls matched for age, sex and geographical area. Disease activity and accumulated organ damage were assessed in the SLE patients.

Results—The SLE patients had significantly lower BMD values at lumbar spine L2-L4 and hip, and higher frequency of osteoporosis at all sites of measurement compared with matched healthy controls. The matched SLE and RA patients had similar BMD, prevalence of osteoporosis and reduced bone mass. In the SLE patients BMD was more strongly correlated with accumulated organ damage than with markers of disease activity or duration. In multivariate analyses BMD was at all sites predicted by age and body mass, at lumbar spine also by the current corticosteroid dose.

Conclusion—The study showed reduced BMD in patients with SLE compared with matched healthy controls. Premenopausal women taking corticosteroids were especially affected. Furthermore, the BMD of matched SLE and RA patients was reduced to a similar extent.


Improved survival of systemic lupus erythematosus (SLE) patients over the past decades has put morbidity as outcome measure into focus. Osteoporosis (OP) contributes to morbidity in SLE, and OP with fractures is one of the items in the accumulated organ damage index (SDI) for the disease.

OP, characterised by a reduction in bone mineral density (BMD), microarchitectural deterioration of bone tissue, increased bone fragility, and consequently increased risk of fractures may be related to the underlying disease process in SLE, its treatment or the risk factors in the general population.

Although a large body of data on OP in RA has emerged, literature investigating OP in SLE is practically non-existing, and many previous studies of OP in SLE have used older methods, making comparison to newer studies difficult. Dual energy x ray absorptiometry (DEXA) has been used in some studies in SLE. The majority of these have been limited to small samples of premenopausal women. OP in SLE has previously been compared with healthy controls and with RA. However, none of the studies comparing SLE and RA have used DEXA. Moreover, examination of BMD measured by DEXA has not been applied in studies comparing SLE, RA and healthy controls at the same time.

The main objective of this study was therefore to examine BMD in SLE patients, using DEXA, and to compare BMD in SLE patients with two control groups, one comprising by age and sex matched healthy controls and one by age, sex and disease duration matched patients with rheumatoid arthritis (RA). We further intended to study the relations between BMD, demographic and disease variables in the SLE patients.

Methods

SETTING
The study was performed at Diakonhjemmet hospital, Oslo City Department of Rheumatology, which offers rheumatological service for the community of Oslo, the capital city of Norway with approximately 500 000 inhabitants. Previous studies have demonstrated that the community of Oslo serves as a reliable setting for the performance of epidemiological studies in rheumatology.15 16

PATIENTS AND HEALTHY CONTROLS
A cohort of 93 SLE patients fulfilling the revised classification criteria for SLE, and with residential address in Oslo, has been followed up longitudinally since 1995/1996. Eighty seven of them participated in a follow up examination in 1997–98, of whom patients ≤ 70 years (n=80) were eligible for this study. Five refused to participate, leaving 75 patients for inclusion in the study. The five non-participants did not differ from the participants regarding demographic and disease variables.

Seventy five RA patients6 matched to the SLE patients for sex, age and disease duration (± 2 years) were recruited from the Oslo RA...
register at Diakonhjemmet Hospital. The register was established in 1991, comprising patients with RA with disease onset after the age of 16 years and with a residential address in Oslo.19

People used as healthy controls were selected from the Population register of Oslo. Each control was matched to one of the SLE patients with regard to age, sex and geographical area of Oslo, consistent with a case-control design of the study. The healthy controls received an invitation by mail, and the initial nonrespondents received a reminder after two weeks. None of the healthy controls had rheumatic disease or used corticosteroids for other health conditions.

DATA COLLECTION AND CLINICAL MEASURES
The SLE, RA patients and healthy controls consenting to participate were examined at the outpatient clinic by a standardised interview and BMD. The assessments of the SLE patients were performed in 1997–1998, and RA patients in 1996–97 and the healthy controls in 1998.

Data collected from the interview included menstrual status, age at and duration of menopause, smoking habits and previous osteoporotic fractures. Data on physical disability were collected by self reported questionnaires (Modified Health Assessment Questionnaire (MHAQ))19 and SF-3620 filled in the day before or during the visit. MHAQ is a modified shortened version of the Stanford Health Assessment Questionnaire,21 examining eight dimensions of difficulties with the performance of activities of daily living, scaled 1–4. SF-36 physical is the physical part of the generic instrument, MOS Short Form SF-36, measuring eight dimensions of health status.22 The scales of SF-36 are expressed with values from 0 to 100, with higher value representing better functioning/health. The version covering the past four weeks was used.

The SLE and RA patients underwent a clinical examination and a careful review of their medical records, performed by one of us (IMG) for the SLE patients and by a trained research nurse in collaboration with a rheumatologist for the RA patients. Number of tender and swollen joints was assessed by the 28 joint count in both patient groups.

Disease activity in the SLE patients was assessed by the SLE disease activity index (SLEDAI),22 and accumulated organ damage by the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage index (SDI).17 The SLEDAI is a validated disease activity measure index. The version covering the past 10 days was used. It contains 24 descriptors in nine organ systems, including clinical and laboratory measures of SLE activity, and is weighted to reflect the degree of activity. The maximum possible score is 105. The SDI is designed to assess accumulated organ damage in the SLE since onset of the disease, caused by the disease itself or the treatment. Damage is defined for 12 organ systems and the score can only increase over time, theoretically to a maximum of 47.

Disease onset was defined as the time when the patients fulfilled the ARA/ACR criteria for the respective diseases (SLE and RA); disease duration as the period from the disease onset to the time of this study.

BONE MINERAL DENSITY MEASUREMENT
BMD of the lumbar spine (L2-L4) and the left hip (femoral neck and total hip) was measured by DEXA equipment (Lunar Expert, Madison, Wisconsin), and expressed in g/cm². The machine was calibrated daily with a spine phantom provided by the manufacturer. The measurement was assessed according to standard procedures. The spine was investigated with the patients in a supine position, straightening the lordotic curvature by elevating the legs with help of a squared pillow (hip and knee flexion 90 degrees). Measurements of the hip were performed with the patient’s left foot in a fixture to position the femoral neck parallel to the table. In two RA patients, the right hip was measured, because of prosthesis in the left.

The spine phantom precision error calculated as a coefficient of variation (CV%) was 0.9% for the whole period (1996 to 1998). The in vivo reproducibility of BMD measurements was assessed from duplicate measurements in 31 healthy female hospital workers (mean age 56.1 years, range 50–66). The precision was 2.5% at lumbar spine L2-L4, 1.5% at total hip and femoral neck. The inter-observer precision variation was 0.7–1.4% for spine L2-L4, 0.4–0.5% for the total hip and 0.5–0.8% for the femoral neck.

DATA ANALYSES AND STATISTICS
The BMD in SLE was compared with BMD of matched RA and matched healthy controls. BMD was also expressed as T score (number of standard deviations (SD) from the mean of young women attaining peak bone mass) and Z score (number of standard deviations of age matched controls adjusted for weight), using the normative German reference values provided by the manufacturer. Osteoporosis was defined according to the conventional WHO definition T score < −2.5 SD,23 and reduced bone mass as T score and Z score below −1 SD.

All statistical analyses were performed by SPSS version 8.0. Descriptive statistics are presented as means with range, standard deviation (SD) or 95% confidence intervals (CI). Group comparisons were analysed by one-way variance (ANOVA) with Bonferroni corrections. F ratios for group comparisons and overall p are presented. t Tests for independent samples were used to compare the means of two groups. Categorical variables were compared by χ² test. The differences were regarded as statistically significant when p < 0.05 and highly significant when p < 0.01. Bivariate relations were examined by Pearson's correlation coefficients and t tests. A correlation between continuous variables was considered as strong if the correlation coefficient was 0.70 or higher, moderate to substantial if between 0.30–0.70, and weak if below 0.30. Predictors of BMD in SLE was first examined by bivariate
The proportion of SLE patients using or having used corticosteroids and the cumulative corticosteroid dose was significantly higher in SLE compared with RA patients, and the duration of corticosteroid treatment somewhat longer in SLE. As expected, the RA patients used significantly more non-steroidal anti-inflammatory drugs (NSAIDs). The use of disease modificating antirheumatic drugs (DMARDs) and cytotoxic drugs was similar in the two groups (table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Descriptive characteristics of the study populations. (Mean (range) for continuous, % for categorical variables)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLE (n=75)</td>
</tr>
<tr>
<td>Women</td>
<td>88</td>
</tr>
<tr>
<td>Age (y)</td>
<td>45 (20–70)</td>
</tr>
<tr>
<td>White</td>
<td>100</td>
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<tr>
<td>Disease duration (y)</td>
<td>8.1 (2–27)</td>
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<tr>
<td>Body mass index</td>
<td>23.5 (17.7–37.6)</td>
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<tr>
<td>Smokers (current or previous)</td>
<td>68</td>
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<tr>
<td>Menopause</td>
<td>43</td>
</tr>
<tr>
<td>Oestrogen replacement therapy</td>
<td>24</td>
</tr>
<tr>
<td>Current users</td>
<td>60</td>
</tr>
<tr>
<td>Mean current dose</td>
<td>7.4 (2.5–20)</td>
</tr>
<tr>
<td>Cumulative dose (g)</td>
<td>21.8 (0.23–113.4)*</td>
</tr>
<tr>
<td>Duration, months</td>
<td>72.6 (1–364)</td>
</tr>
<tr>
<td>Current NSAIDs</td>
<td>17*</td>
</tr>
<tr>
<td>Current cytotoxic drugs</td>
<td>19</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>88*</td>
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<tr>
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<td>17*</td>
</tr>
<tr>
<td>Current DMARDs</td>
<td>35</td>
</tr>
<tr>
<td>Current cytotoxic drugs</td>
<td>19</td>
</tr>
</tbody>
</table>

* p<0.05 SLE v RA. ** p<0.001 SLE and/or RA v healthy controls. NA: not applicable, MHAQ: Modified Health Assessment Questionnaire, SLEDAI: SLE Disease Activity Index, SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, NSAID: non-steroidal anti-inflammatory drug, DMARD: disease modifying antirheumatic drug.

** Results **

As shown in table 1 the study populations comprised 75 SLE patients, 75 matched RA patients and 75 matched healthy controls. Eighty eight per cent of the patients and controls were women. The matched SLE, RA patients and healthy controls were all white and did not differ significantly with respect to body mass index (BMI) and smoking habits. A higher proportion of the SLE patients was menopausal, but the difference between the groups did not reach statistical significance. The use of oestrogen replacement therapy was similar in the three groups. The proportions of patients and healthy controls reporting osteoporotic fractures including Colles fracture were somewhat higher in the SLE group. Number of tender and swollen joints as well as scores of physical disability were, as expected, significantly different in SLE and RA, in the direction of poorer health in RA. Both patient groups were significantly more physically disabled than healthy controls.

** Table 2 **

<table>
<thead>
<tr>
<th></th>
<th>SLE (n=75)</th>
<th>RA (n=75)</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Lumbar spine L2-L4</td>
<td>1.12**</td>
<td>1.08, 1.16</td>
<td>1.17</td>
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<tr>
<td>Femoral neck</td>
<td>0.92*</td>
<td>0.88, 0.95</td>
<td>0.92*</td>
</tr>
<tr>
<td>Total hip</td>
<td>0.94*</td>
<td>0.91, 0.98</td>
<td>0.94*</td>
</tr>
</tbody>
</table>

* p<0.05 SLE v RA v controls (Bonferroni). ** p<0.01 SLE v RA v controls (Bonferroni). †ANOVA.

** Table 2 **

Mean BMD values with 95% confidence intervals in SLE, matched RA patients and healthy controls

** ETHICS AND LEGAL ASPECTS **

The local ethical committee had approved the study and the Data Inspectorate the register of SLE and RA patients in Oslo.

The frequency of SLE patients with osteoporosis (T scores < −2.5 SD) was overall higher compared with healthy controls, but the differences did not reach statistical difference (9% versus 4% at lumbar spine, 7% versus 3% at femoral neck and 4% versus 0% at total hip, SLE versus healthy controls, respectively). The proportion of SLE patients having reduced bone mass (T score < −1 SD) was significantly higher at femoral neck (41% versus 22%) compared with healthy controls, whereas the increased proportions were not significantly increased at lumbar spine (37% versus 28%), at total hip (33% versus 20%) SLE versus healthy controls, respectively. The frequency of SLE patients with osteopenia (T scores < −1 SD) was overall higher compared with healthy controls, but the differences did not reach statistical difference (9% versus 4% at lumbar spine, 7% versus 3% at femoral neck and 4% versus 0% at total hip, SLE versus healthy controls, respectively). The proportion of SLE patients having reduced bone mass (T score < −1 SD) was significantly higher at femoral neck (41% versus 22%) compared with healthy controls, whereas the increased proportions were not significantly increased at lumbar spine (37% versus 28%), at total hip (33% versus 20%) SLE versus healthy controls, respectively. The proportion of SLE patients having Z score < −1 SD was higher than the expected 16% (because of the normal distribution) at all sites and ranged from 21% at the total hip to 29% at lumbar spine, significantly increased at lumbar spine. The healthy controls ranged from 12% to 15%, comparing well with the normal distribution (data not shown).

** COMPARISON OF SLE AND RA PATIENTS **

The SLE patients had similar BMD values at lumbar spine L2-L4, at femoral neck and total hip, compared with sex, age and disease duration matched RA patients (table 2).
Furthermore, no significant differences in BMD appeared when comparing subgroups stratified for their menopausal status (data not shown). Furthermore, the overall frequencies of OP and reduced bone mass were similar. In SLE, the frequency of OP ranged from 4% at total hip to 9% at lumbar spine, in RA from 4% at total hip and femoral neck to 5% at lumbar spine (data not shown).

Reduced bone mass (T score < −1 SD) ranged from 33% to 41% in SLE and 28% to 44% in RA at different sites, whereas the proportion of SLE and RA patients with Z score value < −1 SD was higher than the expected 16%, and ranged from 21% to 29% in SLE and from 16% to 29% in RA (data not shown).

In a multivariate analysis of the relation between BMD at different sites of measurement (dependent variables) and disease status (SLE, RA, healthy controls) as independent variables, the disease status of SLE appeared as an independent significant predictor of BMD at lumbar spine, when controlling for other independent variables (BMI, SF-36 physical, MHAQ, cumulative corticosteroid dose, smoking status and menopause in women). RA disease status had no independent predictive effect on BMD at any site of measurement (data not shown).

ASSOCIATION BETWEEN BMD, DEMOGRAPHIC AND DISEASE VARIABLES IN SLE

Results of bivariate relations of BMD at spine L2-L4 and femoral neck with continuous (Pearson) and categorical variables (r test) are shown in table 3. As expected, age and BMI correlated with BMD both at the lumbar spine and at the femoral neck (data for total hip are not shown as they appeared similar to femoral neck). Accumulated organ damage index score (SDI) correlated moderately with BMD at femoral neck (r = −0.33) and weakly to BMD at lumbar spine (r = −0.26). Menopause in the women was associated with a lower BMD at both lumbar spine and femoral neck (p < 0.01 to 0.03). BMD in current corticosteroid users were significantly reduced at lumbar spine (p = 0.04), but not at femoral neck. Current and cumulative corticosteroid doses correlated weakly to moderately with BMD, whereas duration on corticosteroids showed less correlation. Men had a significantly higher BMD at femoral neck compared with women, whereas no significant difference was found at lumbar spine. Disease duration, disease activity assessed by SLEDAI and history of smoking were not significantly related to the BMD values (table 3).

Linear regression analyses were performed to identify the most important variables predicting BMD at different sites of measurement in SLE. Eligible independent variables were demographic (age, sex, BMI, smoking), disease variables (disease duration, current and cumulative corticosteroid dose, SLEDAI, SDI). As disease activity, disease duration and smoking appeared not to be associated with BMD in univariate analyses these variables were excluded in the multivariate model. The results of the multivariate analyses are shown in table 4. Age, BMI and current corticosteroid dose were all independent significant predictors of BMD at the lumbar spine, and together explained 22% of the variance of BMD, whereas BMD at femoral neck (table 4) and total hip (data not shown) was significantly predicted by age and BMI only.

Discussion

Our data demonstrate that the Norwegian SLE patients had significantly reduced BMD values at lumbar spine and hip compared with sex, age and geographical area matched healthy controls and similar values to that of sex, age and disease duration matched RA patients. The result indicates that SLE or its treatment have pervasive negative impact on BMD. Both trabecular (spine L2-L4) and mixed cortical and trabecular bone were affected causing generally reduced bone mass. Premenopausal women on corticosteroids were especially affected, whereas BMD values in patients never treated with corticosteroids approached matched healthy controls, indicating great impact of corticosteroid treatment on BMD in SLE.
Our findings corroborate previous studies of SLE, showing significantly reduced bone mass at lumbar spine and hip compared with healthy controls. In contrast with our study, Dhillon and coworkers did not find reduced BMD at lumbar spine L1-L4 in premenopausal SLE patients taking corticosteroids for six months or longer compared with healthy controls. Hansen and coworkers found reduced BMD at femoral neck and hand, but normal values at the spine and distal forearm, whereas Li et al found BMD at femoral neck comparable to healthy controls. The conflicting results may be explained by different patient selection, as only premenopausal SLE patients with corticosteroid treatment were examined in some of the studies. Limiting the value of direct comparison to ours.

The occurrence of OP in SLE was higher at all sites of measurement compared with matched healthy controls; the proportions comparing well with other prevalence studies of OP in white patients with SLE and was, as expected, higher than that of 4–6% in Chinese SLE patients. The proportion of patients with reduced bone mass was in line with that of an Australian study.

Our study showed no significant differences in BMD values, frequencies of OP or reduced bone mass between matched SLE and RA patients at any site of measurement. The similar BMD values are interesting in view of the clearly documented impact of RA on BMD. The factors provoking reduced BMD may, however, be different in the two diseases. In RA, reduced bone mass is mainly caused by the underlying inflammatory process, physical inactivity and corticosteroid treatment. Physical disability is found to be less pronounced in SLE than in RA, because of milder inflammation in the joints, and hence less structural damages, which also is in accord with our findings. SLE patients are more extensively exposed to corticosteroids compared with RA, as indicated by the present data (table 1). In SLE, factors other than corticosteroids such as avoidance of sun exposure, renal dysfunction, anticoagulation treatment (heparin or warfarin), ovarian dysfunction, premature menopause and avoidance of oestrogen replacement in women may also be important. In this study a small proportion of the SLE patients had renal disorder (18%) or used anticoagulants (5%). A higher proportion of the SLE patients was postmenopausal compared with the control groups, however, the use of oestrogen replacement therapy was similar in the three groups. The premature menopause in SLE patients could reflect the disease itself, its treatment or both. In addition, patients with SLE may not attain an optimum peak bone mass at skeletal maturity, as their disease often starts in early adult life. Finally, in both SLE and RA, studies suggest that inflammatory factors may change bone metabolism and contribute to the development of OP. Although similar BMD values in SLE and RA may confer similar risk of fractures, the SLE patients recorded somewhat higher proportion of previous osteoporotic fractures compared with RA (table 1). Increased vertebral and hip fracture rates are known in RA and in women with SLE. Reduced BMD values are in general a strong risk factor for fractures in primary OP, but it is not known if this is also the case in secondary OP. Indeed, the study of Peel et al of corticosteroid treated postmenopausal RA patients, showed that the decrease in lumbar spine BMD was less than expected in patients with fractures compared with those without. More studies are needed to clarify the role of BMD as predictor of later fracture in both RA and SLE.

Three previous studies have compared bone mass in SLE and RA, and showed conflicting results, however none of them used DEXA for measurement. In line with our study Dykman et al found no difference in proportions of glucocorticoid induced osteopenia and bone fractures in SLE and RA patients whereas Kalla et al observed significantly reduced bone mass in RA patients only when performing radiometry in premenopausal SLE, RA and healthy controls. Kalla et al also observed more severe periosteal resorption by metacarpal measures in SLE, in contrast with endosteal resorption in RA, suggesting differences in the mechanism of osteoporosis in the two diseases.

The predictive role of BMD and BMI on BMD in SLE corroborates previous studies. As expected, current and cumulative corticosteroid doses correlated moderately with BMD at all sites of measurement. The results of the multivariate analysis confirmed that the current dose independently predicted BMD at lumbar spine, supporting that trabecular bone may be more sensitive to corticosteroids than cortical bone. The negative impact of corticosteroids on bone mass corroborates some studies and contrasts others. These discrepancies are unclear, but different practice in use of corticosteroids may have an explanation. BMD values correlated better with accumulated damage (SDI) than with disease activity (SLEDAI) (table 3). Both BMD and organ damage capture cumulative changes over time, in contrast with disease activity recording new or deteriorating disease activity the last 10 days. The lack of correlation between BMD, disease duration and disease activity agrees with previous studies.

Limitations of this study are the relatively small patient samples, lack of data on biochemical and hormonal parameters relevant to reduced bone mass in SLE and RA, lack of analysis of spinal deformities and lack of data using hand as a possible site of measurement. Data on structural damage—that is, radiographic abnormalities in RA patients was not available. Strength of our study is the successful demographic matches of the study populations, permitting a case-control design. When matching SLE and RA patients, we controlled for two independent and important variables, namely age and disease duration. The higher proportion of SLE patients with menopause compared with the control groups may, however, skew the BMD data, as menopause has an important impact on BMD. The data of RA patients included from the register are
reasonably representative for the RA population in Oslo,17 and their BMD concurred with that in RA patients aged 40–49 years in that register. The low coefficient of variation of the DXA data assured that standard procedures were followed. The in vivo reproducibility of BMD measurements of duplicate measurements in 31 healthy female hospital workers was also satisfactory.

To conclude, the study showed that our SLE patients had reduced bone mass at all sites of measurement compared with age and sex matched healthy controls. Especially the premenopausal women taking corticosteroids were affected, whereas patients with mild SLE and only corticosteroids used and bone mass values approaching the normal population. Furthermore, the bone mass of matched patients with SLE and RA was reduced to a similar extent.

The study also showed that the SLE patients received more corticosteroids than the RA patients and underwent menopause at an earlier age whereas the RA patients had more severe physical disability. Disease activity and duration did not affect BMD in SLE, whereas corticosteroids did. Clinical implications of this study include emphasis on lowering corticosteroid dose if possible, and prevention and treatment of OP in SLE patients taking corticosteroids.

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Acknowledgments


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