Risk of vertebral fracture and relationship to bone mineral density in steroid treated rheumatoid arthritis

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Abstract

Objectives—To determine the prevalence of vertebral fracture in postmenopausal women with steroid treated rheumatoid arthritis (RA), and whether the risk of vertebral fracture could be predicted from measurements of bone mineral density (BMD).

Methods—Vertebral deformities were defined from spine radiographs in 76 postmenopausal women with steroid treated RA (aged 50–79 years) and 347 age matched women from a population based group, using a morphometric technique. Lumbar spine (LS) BMD was measured by dual energy x ray absorptiometry.

Results—The odds ratio for vertebral fracture in the women with RA was 6·2 (95% confidence interval 3·2 to 12·3). The decrease in LS-BMD was less than expected for the observed prevalence of vertebral fracture and, among the women with RA, LS-BMD was not lower in those with vertebral fractures.

Conclusions—We conclude that patients with steroid treated RA may have abnormal bone quality, and that LS-BMD cannot be used to predict the risk of vertebral fracture in these patients.

Bone loss is a well recognised complication of rheumatoid arthritis (RA) and is not only localised around inflamed joints, but also affects skeletal sites distant from them, such as the lumbar spine and proximal femur. The aetiology of bone loss is likely to be multifactorial. Studies have demonstrated that disease activity is a determinant of bone loss in RA and may be mediated by the release of bone resorbing cytokines such as interleukin-1 (IL-1) and tumour necrosis factor (TNF) from the inflamed synovium. Other determinants of bone loss in RA may include physical inactivity, weight loss, and the use of drugs such as corticosteroids.

In type I osteoporosis, the risk of vertebral fracture has been shown to increase two- to threefold for every SD decrease in bone mineral density of the lumbar spine (LS-BMD) below the expected value. The risk of vertebral fracture may therefore be expected to be increased in RA. Because vertebral fractures may be asymptomatic, their prevalence can only be determined from radiological surveys. Spector et al recently reported that the rate of vertebral fracture was increased in postmenopausal women with RA, some of whom were treated with oral corticosteroids, but that BMD of the lumbar spine and femoral neck was not lower in the women with vertebral fracture. They did not compare BMD of the women with RA and the controls. Their results suggest that the relationship between vertebral fracture risk and BMD may differ in secondary osteoporosis compared with type I osteoporosis.

The aims of this study were to determine the prevalence of vertebral fracture in postmenopausal women with RA who had been treated with corticosteroids, in comparison with population based controls, and to determine whether BMD measurement could predict the risk of vertebral fracture in these women.

Subjects and methods

We studied 76 postmenopausal women with RA (ages 50–79 (mean 65) years), and 347 women from a population based group (ages 50–79 (mean 64) years) as controls. There was no difference in menopausal age between the groups (mean time since menopause 16 years in the RA group compared with 18 years in the controls). None of the 76 women in the RA group was receiving hormone replacement therapy (HRT) at the time of the study, compared with 19 of the 347 controls (5·5%). None of these 19 was included in the group of 20 women comprising the BMD controls (see below).

Each subject gave informed consent and the study was approved by the ethics committees of the Royal Hallamshire Hospital and the Northern General Hospital, Sheffield.

POSTMENOPAUSAL WOMEN WITH RA

The women with RA were invited to participate in a clinical study of bisphosphonate treatment for the prevention of bone loss. The inclusion criteria for the study were that they were white, postmenopausal, had a diagnosis of rheumatoid arthritis (as defined by the American Rheumatism Association 1987 criteria) in functional grades I–III, and had received corticosteroid treatment for at least six months. Postmenopausal status was defined as...
more than six months having elapsed since their last menstrual period, together with appropriate serum concentrations of oestradiol and follicle stimulating hormone. The disease duration in the women studied ranged from three to 45 years (>15 years in 90%), and they had all received treatment with prednisolone for between one and 40 years (mean current dose 4-7 mg/day; 85% of subjects had received steroid treatment for >10 years). The majority of patients were treated at a dose of 2-5 or 5 mg/day, and four had received doses greater than 10 mg/day for short periods in the past. The cumulative dose of steroid ranged between 2-5 and 79 g (mean 28.8; median 27.0 g).

Subjects were excluded if they had evidence of secondary causes of osteoporosis other than RA or steroid treatment (all had normal results for serum calcium, phosphate, alkaline phosphatase, creatinine, thyroxine, thyroid stimulating hormone and parathyroid hormone (PTH), and 24 hour urine calcium excretion), or a history of any other acute or chronic medical condition likely to affect BMD. Subjects were also excluded if they had received previous treatment with drugs known to influence bone turnover.

All women fulfilling these criteria who attended outpatient clinics of one consultant rheumatologist (DEB) over a 10 month period were invited to attend for a screening assessment, at which time the clinical assessment was made, and spinal radiographs were obtained. The uptake rate from these clinics is unknown.

Among the women with RA included in this study, 19 were currently receiving disease modifying antirheumatic drugs (DMARDs) (sulphasalazine seven; IM sodium aurothiomalate eight; hydroxychloroquine two; methotrexate two), 38 were currently receiving non-steroidal anti-inflammatory drugs (NSAIDs), and 60 were receiving simple analgesics.

DEFINITION OF VERTEBRAL FRACTURE
Each subject had anteroposterior (AP) and lateral radiographs of the thoracic and lumbar spine, taken at a standard target to film distance of 100 cm. Thoracic films were centred on vertebra T7 and lumbar films on vertebra L2. Vertebral deformities were defined according to the morphometric criteria of Eastell et al.17 In this method the anterior (ha), posterior (hp) and mid (hm) height of each vertebra from T4 to L5 are measured on the lateral radiographs and deformities defined for each vertebra as:

\[
\% \text{ wedge} = \frac{hp-ha}{hp} \times 100
\]
\[
\% \text{ biconcavity} = \frac{hp-hm}{hp} \times 100
\]
\[
\% \text{ compression} = \frac{hp-h'}{hp} \times 100
\]

where hp' is the posterior height of the vertebra below or the vertebra above. The deformities for each vertebra were compared with published normative data from women17 and a vertebra was considered to be fractured if it had a deformity more than 3 SD less than the mean for that vertebra.

Marking of the radiographs was performed by a single observer. The AP radiographs were used to identify the vertebra and to take account of anomalous segmentation which we have shown to affect 16-5% of individuals.18 Radiographs were assessed for the presence of vertebral deformities resulting from fracture or other causes, by a consultant radiologist (NAB, DJM) blind to the results from the morphometric analysis of the radiographs.

POPULATION BASED (CONTROL) GROUP
A cohort of 375 women aged 50–85 years had been selected randomly from a population based group from three general practice lists in Sheffield (uptake rate 55%) and were taking part in a study of the prevalence of osteoporosis. From this cohort, we took the 347 women younger than 80 years to comprise our control group for the prevalence of vertebral deformities. Because the densitometer used in the population based study differed from ours, invalidating any direct comparison of BMD values between the studies, 20 healthy women from the population based cohort were selected as a control group to create our own reference range of BMD values. The original BMD Z scores at each skeletal site in these 20 women had been representative of their population based group (see below). They were selected from the larger cohort on the basis that they had no evidence of arthritis on history or examination, and no evidence of significant degenerative change on spinal radiographs. None had received drugs known to affect bone metabolism, and biochemical screening excluded diseases likely to affect bone metabolism (serum thyroxine, calcium, phosphate, alkaline phosphatase, PTH and creatinine, and 24 hour urine calcium excretion all within normal limits).

BONE DENSITOMETRY
BMD of the lumbar spine, femoral neck (FN-BMD), and total body (TB-BMD) were measured by dual energy x ray absorptiometry (Hologic QDR 1000/W, Hologic Inc, Waltham, MA) in all the women with RA and the 20 healthy women from the population based group (aged 54–77 (mean 63) years). The reproducibility of BMD measurements using the Hologic QDR 1000/W was assessed from duplicate measurements in 20 women aged 27–77 years, of whom 12 had RA. The precision error, calculated as a coefficient of variation, was 1.4% at the lumbar spine, and 2.9% at the femoral neck. Vertebræ which were identified as being fractured within the region of analysis (L1 to L4) were excluded from the analysis to avoid artificial over-estimation of measured LS-BMD.

The BMD of the 20 healthy controls, measured previously using a different densitometer (Lunar DPX, Lunar Corp, Madison WI) was representative of the 375 women in the population based group from which they were selected (mean Z scores normalised for age and weight: -0.01, 95% confidence interval
Vertebral fractures in steroid treated RA

Table 1  Prevalence of vertebral deformities in women with steroid treated rheumatoid arthritis compared with population based controls

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Rheumatoid arthritis</th>
<th>Population</th>
<th>Rate</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vdef (No)</td>
<td>No Vdef (No)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>50–59</td>
<td>4</td>
<td>9</td>
<td>30-8</td>
<td>1</td>
</tr>
<tr>
<td>60–69</td>
<td>11</td>
<td>33</td>
<td>25-0</td>
<td>9</td>
</tr>
<tr>
<td>70–79</td>
<td>6</td>
<td>13</td>
<td>31-6</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>55</td>
<td>27-6</td>
<td>20</td>
</tr>
</tbody>
</table>

Vdef = Vertebral deformities; diff = difference; CI = confidence interval; OR = odds ratio.

(Or) -0.4 to 0.4 for TB-BMD; -0.14, 95% CI -0.4 to 0.2 for LS-BMD; 0.00, 95% CI -0.4 to 0.4 for FN-BMD). Mean LS-BMD measured using the Lunar DPX did not differ between the 20 controls and the entire population based group (1.041 ± 1.069 g/cm²), but the SD was smaller in the 20 controls (0.12 ± 0.19 g/cm²; F ratio 2.68; 95% CI 1.24 to 4.73).

STATISTICAL ANALYSIS
The proportions of women with vertebral fractures were compared by calculation of odds ratios and 95% confidence intervals.19 Differences in BMD were examined by comparison of Z scores (expressed as SD units from the expected value) using t tests and analysis of variance. Scheffé test was used to test for heterogeneity between groups. The relationship between normally distributed variables was examined using Pearson’s correlation coefficients. Precision was calculated as the ratio of SD of duplicate measurements to mean BMD, expressed as a percentage. Analyses were performed using Statgraphics Statistical Graphics System (Statistical Graphics Corporation, Rockville, MD).

Results

VERTEBRA FRAC TURE RATES
Table 1 shows the vertebral deformity rates, defined using the morphometric algorithm, in the women with steroid treated RA and the population based controls. In the group as a whole there was an increased prevalence of vertebral deformities (odds ratio 6.2, 95% CI 3.2 to 12.3) that was most marked in women aged 50–59 years. Radiological assessment suggested that eight of the deformities defined by the algorithm (20% four in the RA group, and four in the control group) were the result of pathology other than vertebral fracture. These were parallax errors resulting from severe scoliosis (five), Scheuermann’s disease (two) and spondylolisthesis (one). The prevalence of vertebral deformity believed to result from pathology other than fracture was 1% in the controls and 5% in the women with RA (NS: 95% CI of difference, -9 to 1%).

Vertebral deformities both in women with RA and in controls were evenly distributed between the thoracic and lumbar spine. In the women with RA, 63% of deformities were of thoracic vertebrae, and in the controls, 61% of deformities were of thoracic vertebrae. This reflects the proportion of vertebrae assessed (T4 to L5, of which 64% were thoracic).

Table 2 shows the number of subjects with single and multiple vertebral deformities. In the women with RA the number of these deformities did not relate to factors such as BMD, age, height, weight, disease duration, or steroid treatment (mean daily or cumulative dose, or duration of treatment).

Table 2  Number of vertebral deformities per subject in 76 women with steroid treated rheumatoid arthritis (RA) and 347 age matched women from a population based group

<table>
<thead>
<tr>
<th>Number of deformities</th>
<th>RA</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>55</td>
<td>327</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3 shows the decrease in BMD in the women with RA compared with the healthy controls, and the figure illustrates the decrease in BMD expressed as Z scores. The BMD in RA was decreased by 10–16%, or 0.8–1.5 SD units: the mean (95% CI) Z scores were -0.79 (-1.05 to -0.51) (lumbar spine), -1.15 (-1.36 to -0.94) (neck of femur), and -1.46 (-1.81 to -1.11) (total body). There was no difference in BMD at any site between those women with and without vertebral deformities (table 3), and the women with deformities did not differ from those lacking them with respect to age, height, weight, disease duration, or steroid treatment (mean daily or cumulative dose, or duration of treatment).

In the women with RA, LS-BMD correlated with body weight (r = 0.39, p < 0.001), which was lower than that of healthy controls (58.7 ± 6.6 kg; 95% CI of difference -10.7 to -1.1 kg). In a multiple linear regression model,
the effect of weight and the presence or absence of RA was examined for each of the BMD measurement sites. There was a significant effect of RA at each site after correction for weight (LS-BMD, \( p = 0.05 \); FN-BMD, \( p < 0.0001 \); TB-BMD, \( p < 0.0001 \)).

Disease activity, assessed by erythrocyte sedimentation rate, correlated with LS-BMD \( (r = -0.28, p = 0.02) \). There was no correlation between BMD, at any site, and age. There was no correlation between BMD and disease duration, duration of steroid treatment, or daily or cumulative dose of corticosteroid. Multiple linear regression did not demonstrate an effect of current DMARD, NSAID or analgesic treatment on BMD measurements or fracture risk.

### Discussion

This study suggests that postmenopausal women with steroid treated RA are at increased risk of vertebral fracture, but the proportions of risk attributable to the disease itself or to the concomitant steroid treatment cannot be determined from our data. The greatest risk of vertebral fracture appeared to be in the younger women with RA, but the number of patients younger than 60 years was small, as is reflected by the wide confidence limits for the odds ratio. The distribution of vertebral deformities between the thoracic and lumbar vertebrae did not differ between the groups, and the numbers of subjects with multiple vertebral deformities were similar (table 2).

The increased risk of fracture is in agreement with the one previous study in which morphometric criteria were used to define vertebral fractures in RA.\(^{14}\) The lower odds ratio for vertebral fracture in that study may reflect the fact that only 34% of the women in the study were receiving corticosteroids, though we have found no association between BMD and duration of steroid use, mean daily dose, or cumulative dose, and no difference in steroid use between the women with and without vertebral fractures.

The high odds ratio for vertebral fracture could also result from an underestimate of the prevalence of vertebral deformities in the control population. However, the marking of the radiographs of both the patients and controls was performed by a single individual, and the prevalence of vertebral deformities identified by the morphometric algorithm was in very close agreement with the prevalence rates defined by experienced radiologists (NAB and DJM), who were blind to the results of the morphometric analysis. The prevalence of vertebral deformities within the population based group was also very similar to that established in another UK population using the same morphometric algorithm.\(^{20}\)

In type I osteoporosis, we would expect an odds ratio for vertebral fracture risk greater than 6 to be associated with a decrease in LS-BMD of 2–3 SD, yet in this cohort of women with steroid treated RA, the LS-BMD was decreased by only 0.79 SD. As the SD of the LS-BM measurements was significantly smaller in our control group compared with the population from which they were selected, there may be an overestimate of the Z score. The smaller decrease in LS-BMD than expected for the prevalence of vertebral fracture and the fact that there was no difference in LS-BMD between the women with and without vertebral fractures, could be artefactual or could reflect defective bone quality in the women with steroid treated RA. Alternatively, it may reflect the impact on the skeleton of other factors associated with RA, such as the increased tendency of patients with arthritis to fall,\(^{21}\) or altered biomechanics of the spine resulting from these patients' multiple deformities.

Our results could have been explained if a high proportion of the vertebral deformities defined by the morphometric algorithm in the women with RA were the result of pathology other than vertebral fracture. However, review of the spine radiographs by consultant radiologists did not support this idea. Similarly, there may have been a high proportion of traumatic vertebral fractures, which would not necessarily be associated with low BMD. Although this is not easy to quantify, there was no supporting evidence from the case records.

Another possibility was that the women with vertebral fractures had more severe degenerative disease of the spine which led to an artefactual increase in LS-BMD. This concept was not supported by review of the spine radiographs, and after exclusion of subjects with significant degenerative change of the lumbar spine from the analysis, there remained no difference between the groups.

It has been demonstrated in several studies that in type I osteoporosis BMD measurements are site specific—that is, the fracture risk at a particular skeletal site is best predicted by BMD at that site.\(^{22,23}\) We would therefore expect measurement of LS-BMD to have superior diagnostic sensitivity for vertebral fracture than measurement of FN-BMD or TB-BMD. Nonetheless, the fact that there was also no difference in TB- or FN-BMD between the women with and without fractures (table 3) suggests that the poor diagnostic sensitivity of BMD measurement in steroid treated RA is the
result of heterogeneity in bone quality rather than artefactual problems of LS-BMD measurement in these women.

BMD measurements are believed to reflect approximately 75% of the variability in bone strength,24 bone quality contributes to the remaining 25%; for example, there may be differences in the frequency of trabecular perforation, or in the elasticity of bone. The use of novel techniques of bone measurement such as ultrasound densitometry, which may reflect trabecular architecture, or lateral LS-BMD measurement by dual energy x ray absorptiometry (which may be a more sensitive measure of trabecular bone loss in cortico-steroid induced osteoporosis than the antero-posterior technique we used25), may help to resolve this question.

The design of our study did not permit determination of the independent effects of steroid treatment and RA on the skeleton. There remains no consensus on the effect of low dose corticosteroid treatment on bone mass in RA. Although many studies have shown decreased BMD in RA patients with steroids compared with non-steroid-treated patients,3,5,11 others have failed to demonstrate this.4,26 There is evidence that the deleterious effect of steroids may be restricted to the use of more than 5 mg of prednisolone daily in postmenopausal women with RA, and that doses of up to 7.5 mg daily may not be harmful to bone in premenopausal women and in men with RA.4,15 However, a greater adverse effect of corticosteroids in premenopausal women has been shown,23 while a decreased rate of loss of total body BMC has been demonstrated in patients receiving corticosteroids, despite their having a lower initial normalised bone mass than the non-steroid-treated patients.28 This suggested that the deleterious effect of steroid treatment may occur in the initial phase of treatment.

The possibility also exists that other medication may have influenced the development of osteoporosis and vertebral fractures in the women we studied. Although a multiple linear regression model failed to show either DMARD or NSAID treatment to influence BMD or vertebral fracture prevalence in this cohort, this does not exclude the possibility that these medications may have influenced the skeletal status of these women. Current medication may not be representative of previous medication, particularly in view of the long disease duration in these subjects. Similarly, it is not possible from a cross sectional study to determine the influence of these medications on underlying disease activity.

In summary, we have demonstrated a considerable increase in the risk of vertebral fracture in postmenopausal women with steroid treated RA. The relative effects of corticosteroid treatment and the disease itself could not be determined from this study. Although LS-BMD was significantly decreased in these women, the magnitude of this decrease could not fully explain the increase in risk of vertebral fracture. BMD measurements did not differentiate between women with and without vertebral fractures. We speculate that there may be a bone quality defect in steroid treated RA, perhaps mediated by increased bone turnover and increased trabecular perforation. We conclude that measurement of LS-BMD may not be a useful assessment of fracture risk in this form of secondary osteoporosis.

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