Vertebral Deformities in Rheumatoid Arthritis

A Comparison With Population-Based Controls

Ragnhild E. Ørstavik, MD; Glenn Haugeberg, MD; Petter Mowinckel, MS; Arne Høiseth, MD, PhD; Till Uhlig, MD, PhD; Jan A. Falch, MD, PhD; Johan I. Halse, MD, PhD; Eugene McCloskey, MD, PhD; Tore K. Kvien, MD, PhD

Background: Previous studies have shown an increased prevalence of osteoporosis in rheumatoid arthritis (RA), but the extent of osteoporotic fractures is not clarified. The aim of this study was to compare the prevalence of vertebral deformities in a representative, population-based cohort of female patients with RA with matched controls, and to examine the relationship between deformities and RA, bone mineral density (BMD), and corticosteroid use.

Methods: Female patients (mean age, 63.0 years; range, 50.7-73.6 years) were recruited from a county register of patients with RA. Population controls were matched for age, sex, and residential area. Participants had thoracolumbar radiographs taken according to a standardized procedure, and BMD was measured at the hip and spine (L2-L4).

Results: The overall number of vertebral deformities was substantially higher in the RA group compared with controls (147 vs 51, applying the morphometric criteria), with a highly significant difference between patients and controls regarding the presence of multiple deformities measured morphometrically (11.2% vs 4.8%; odds ratio, 2.60; 95% confidence interval, 1.21-6.04) and moderate or severe deformities measured semiquantitatively (17.3% vs 10.0%; odds ratio, 2.00; 95% confidence interval, 1.11-3.74). In Poisson regression analysis, vertebral deformities were independently associated with RA, BMD, and long-term corticosteroid use.

Conclusions: Vertebral deformities are markedly increased in patients with RA compared with controls, especially regarding severe and multiple deformities. A diagnosis of RA was associated with vertebral deformities independently of BMD and long-term corticosteroid use. These findings have important implications for prevention of established osteoporosis in RA.

Arch Intern Med. 2004;164:420-425
patient population, with individually matched controls, or in groups large enough to explore the presence of multiple deformities or deformities of different severity.

The aim of the present study was to compare the prevalence of vertebral deformities in a representative cohort of female patients with RA with that in individually matched controls, and to explore possible associations between vertebral deformities, on one hand, and the disease, BMD, and corticosteroid use on the other.

PATIENTS AND CONTROLS

The Oslo RA register consists of patients fulfilling the American College of Rheumatology 1987 revised classification criteria for RA\(^1\) who have a residential address in the county of Oslo, Norway. The completeness of the register has been described to be 85%, and details of the register have been extensively described in previous publications.\(^2,3\) The inclusion criteria for this study were enrollment in the Oslo RA register, female sex, white race, disease duration of at least 2 years, and year of birth between 1926 and 1948 (age at least 50 years at study onset).

Patients were invited from a representative subgroup of the RA register that had been included in an epidemiologic study that involved BMD measurements 2 years previously.\(^1,2\) A single control subject for each patient was randomly selected from the population register of Oslo, after matching for age, sex, and residential area. Candidates for controls were invited by letter, and a reminder was sent if no answer was received within a month. If a candidate declined, a second subject was identified.

ANALYSIS OF VERTEBRAL DEFORMITIES

Each subject had anteroposterior and lateral radiographs taken according to a standardized procedure.\(^2,3\) Vertebral deformities were analyzed morphometrically at the World Health Organization Collaborating Centre for Metabolic Bone Diseases in Sheffield, England, applying the McCloskey et al algorithm\(^22,23\) for the identification of vertebral deformities. Briefly, measurements of the anterior (A), central (C), and posterior (P) vertebral heights were captured by means of a semiautomated technique comprising a backlit digitizing tablet and a computer database. The definition of deformity requires the fulfillment of 2 criteria for each of the 3 vertebral height ratios (A/P, C/P, and P/predicted P), with at least one ratio reduced to more than 3 SDs below their expected mean values.

In addition, all radiographs were analyzed semiquantitatively by an experienced radiologist (A.H.), applying the method described by Genant et al.\(^24\) Deformed vertebrae were classified as grade 1 (mild), 2 (moderate), or 3 (severe), representing a reduction in any of the vertebral heights of 20% to 25%, more than 25% to 40%, and more than 40%, respectively. For quality assurance, vertebrae were rescored after 6 months in 90 patients, of whom 50% had at least 1 vertebral deformity. The k score for whether a patient was classified as having any deformity was 0.75, and for moderate or severe deformities, 0.86. Both analyses were performed in a blinded fashion.

BMD ANALYSIS

The BMD measurements of the hip (total hip and femoral neck) and the lumbar spine (L2-L4, anterior-posterior) were performed with the same dual-energy x-ray absorptiometry equipment (Lunar Expert; Lunar Corp, Madison, Wis). Because of technical errors, 1 patient and 3 controls did not have BMD measurements. In 13 patients and 6 controls, no hip measurement was performed because of bilateral hip replacements. T- and z-score estimations were computed from a pooled European-US reference database. Detailed descriptions of the reference database, equations for computing age- and weight-adjusted z-score estimations, and quality control procedures have been published previously.\(^3\)

COLLECTION OF CLINICAL AND DEMOGRAPHIC VARIABLES

All measurements were performed during the years 1998 to 2001. Demographic, patient, and disease characteristics, including conventional RA disease core measurements, were recorded partly by self-reported questionnaires and partly by interview and clinical examination (patients with RA). The latter were performed by a specially trained research nurse (patients with RA) or medical student (control group) in cooperation with a rheumatologist (R.E.O. or G.H.). Joint assessment included 28–swollen joint count, 28–tender joint count, and 18–deformed joint count (patients with RA). The disease activity score was computed by means of the 28-joint count.\(^23\) Patients who had a rheumatoid factor titer of 64 or more measured on at least one occasion during the disease course were considered to be positive for rheumatoid factor.

STATISTICAL ANALYSIS

Osteoporosis was defined as a T-score of 2.5 SDs or less below reference values of young, healthy individuals, and reduced bone mass as a Z-score of 1 SD or less below the age- and weight-adjusted reference values. Differences between patients and controls were analyzed by applying paired t tests (continuous data) or McNemar test for counts. The 95% confidence intervals (CIs) were computed for differences between means and odds ratios (ORs) for paired data. The presence of no, any, or multiple deformities, applying 2 different thresholds for the semi-quantitative results, was used as the criterion for the categorization of patients in the univariate statistical analyses. Such categorization was conducted for each criterion—no, any, or multiple deformities—separately. Multivariate associations were explored in a Poisson regression model. The Poisson distribution can be used to model the distribution of cell counts in a multiway contingency table, appropriate for the present situation. Vertebral deformities (count variable) was set as the dependent variable, and RA diagnosis as well as factors that were both significantly different between the groups and suggested to be important for the developing of vertebral deformities as independent variables. Interaction terms were added for age and BMD and for corticosteroid use and RA status, but they were removed, as they were not significant. The deviance $\chi^2$ was used in assessing the goodness of fit, and the distribution of data seemed to fit the Poisson distribution well, with $P$ values of .50 and above.

The level of significance was set to .05. Statistical analyses were performed with the SPSS program (version 10.0: SPSS Inc, Chicago, Ill). SAS software (version 8.02: SAS Institute Inc, Cary, NC) was used in the Poisson regression. All tests were 2-sided.

ETHICAL AND LEGAL ASPECTS

The local ethical committee approved this study. The Data Inspectorate had previously approved the register of patients with RA in Oslo.
Representativeness of the Patient Cohort

The total number of patients with RA fulfilling the entry criteria was 528, and the final participant rate in this study was 47.2%. The nonattending patients (n = 279 [52.8%]) comprised 154 patients not attending the initial clinical examination, 75 patients not attending the initial BMD examination, and 41 patients not attending the follow-up. In nine cases we were not able to identify suitable controls. The 249 patients finally included in the analyses were slightly younger than those from the RA register who fulfilled the entry criteria and did not participate (mean difference [CI], 1.67 years [0.51–2.79 years]). There were no statistically significant differences regarding disease duration or presence of rheumatoid factor. Among patients who had been seen for clinical examination 2 years previously (n = 358), no statistically significant differences were found between those included in the present study (n = 249) and those who declined attending (n = 109) for the following clinical variables: disability score from modified health assessment questionnaire, disease activity score, prednisolone use, or ever use of disease-modifying antirheumatic drugs. Thus, the patients included were considered fairly representative of the entire underlying patient population in the county of Oslo born between 1926 and 1948.

In addition to the 249 included controls, letters were sent to 168 who either declined (n = 69) or did not respond (n = 99). Thus, the final attendance rate for controls was 39.7%.

Vertebral Deformities

The total number of vertebral deformities detected morphometrically was 147 in the RA group, compared with 51 in the control group. Most deformities were found in the midthoracic and thoracolumbar region of the spine, and the pattern of distribution was similar in both groups (Figure 1). Table 2 shows that the difference between patients and controls became more obvious when patients were categorized into presence of 2 or more deformities instead of any deformity. Fifty-five (22.1%) of the patients with RA compared with 38 (15.3%) of the controls had at least 1 vertebral deformity measured morphometrically (OR, 1.74; 95% CI, 1.02–3.04), and 28 (11.2%) vs 12 (4.8%) had 2 or more deformities (OR, 2.60; 95% CI, 1.21–6.04) (Table 2).

Results were similar when the semiquantitative methods were used (Table 2), except for a higher number of deformities in both patients and controls. The total number of deformities (grade 1 or more) was 181 in the RA group, compared with 86 in the control group. The corresponding numbers for moderate or severe deformities only were 95 and 30, respectively.

Bone Mineral Density

The BMD in patients with RA was significantly reduced compared with that in controls at all 3 measurement sites, in both absolute values and age- and weight-adjusted Z-scores (Table 3). Patients with RA who had a history

| Table 1. Demographic and Disease Characteristics for Patients and Control Subjects |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **No. of Subjects** | **Patients** | **Controls** | **P Value** |
| Age, y | 249 | 63.0 (6.8) | 63.4 (6.7) | <.001 |
| Height, cm | 249 | 164.2 (6.0) | 163.7 (5.9) | .36 |
| Weight, kg | 249 | 66.1 (12.5) | 68.9 (11.9) | .002 |
| BMI | 249 | 24.5 (4.4) | 25.9 (4.2) | <.001 |
| Disease duration, y | 249 | 16.6 (10.4) | NA | |
| RF positive, % | 239 | 51.9 | NA | |
| 28-Joint DAS | 230 | 4.71 (1.24) | NA | |
| MHAQ | 248 | 1.67 (0.55) | 1.11 (0.24) | <.001 |
| Smoking status, % | 239 | 33.1 | 30.1 | .56 |
| Current smoker | 47.8 | 2.4 | <.001 |
| Ever users | 69.5 | 11.1 | <.001 |
| Long-term users† | 53.0 | 2.4 | <.001 |
| Bone-protecting agents, % | 249 | 43.4 | 29.3 | .002 |
| Estrogens | 57.8 | 48.0 | .04 |
| Bisphosphonates | 249 | 12.0 | 1.2 | <.001 |
| Current users | 16.0 | 1.6 | <.001 |
| Ever users | 0.8 | 0.8 | 1.00 |
| Calcium supplement | 249 | 61.8 | 20.9 | <.001 |
| Current users | 73.1 | 26.9 | <.001 |
| Ever users | 72.5 | 57.3 | <.001 |
| Cholecalciferol supplement | 249 | 80.4 | 66.3 | <.001 |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; MHAQ, modified health assessment questionnaire; NA, not applicable; RF, rheumatoid factor.

Values are given as mean (SD) for continuous variables. When variables appear in both pairs, significance of difference was tested with paired t test for continuous variables and McNemar tests for dichotomous variables.

†Ever users for 12 months or more.

Demographic and disease characteristics of patients and controls are given in Table 1. Group differences of importance were found for body weight, body mass index, disability level, use of corticosteroids, and osteoporosis medication. Hypertension was recorded in 16.5% of the patients with RA vs 24.2% of the controls (P = .04); occurrence of other concomitant diseases was similar. Fifty-five (22.1%) of the controls self-reported a rheumatic disease other than RA, most frequently chronic musculoskeletal pain syndromes or osteoarthritis.
of long-term corticosteroid use (ever use of corticosteroids for more than 12 months) had a mean Z-score of −0.56, compared with −0.25 in the remaining patient group (P = .03). Osteoporosis was significantly more common among patients than controls, with ORs ranging from 5.8 (95% CI, 2.4-17.0) at the total hip to 2.0 (95% CI, 1.2-3.4) at the spine (L2-L4) (Table 4).

**RELATIONSHIP BETWEEN BMD AND VERTEBRAL DEFORMITIES**

Figure 2 shows Z-scores for patients and controls with and without vertebral deformities measured morphometrically. The mean total hip Z-score in patients with any vertebral deformity was −0.73, compared with −0.33 in patients without deformities (P = .02). The corresponding values for the control group were 0.30 and 0.02, respectively (P = .20).

**MULTIVARIATE ANALYSIS**

A Poisson regression model was used to explore relationships between BMD, presence of RA, and corticosteroid use on one hand and morphometrically defined vertebral deformities on the other. Diagnoses of RA and BMD were both significantly associated with vertebral deformities (relative risk, 1.90 [95% CI, 1.30-2.76] and 1.53 [95% CI, 1.30-1.81], respectively) when controlling for age, body mass index, and use of estrogens or bisphosphonates. Long-term corticosteroid use was added to the model, the association between RA and vertebral deformities was weaker, but still significant (relative risk, 1.90 [95% CI, 1.30-2.76] and 1.53 [1.30-1.81] and 1.55 [1.03-2.33], respectively).

This study demonstrates that patients with RA have substantially more vertebral deformities than population-based controls. The increased occurrence of deformities is especially apparent when more severe and multiple deformities in individual patients are considered. The second important finding is that, apart from BMD and corticosteroid use, RA in itself is independently associated with vertebral deformities (1.53 [1.30-1.81] and 1.55 [1.03-2.33], respectively).

**COMMENT**

In 1 of the 2 previous studies comparing vertebral deformities in patients with RA with those in non-RA controls, Spector et al18 found that the OR of vertebral deformities in patients with RA was 1.47 [95% CI, 1.03-2.31], and BMD (T-score at the total hip) and corticosteroid use were both significantly associated with vertebral deformities (1.90 [95% CI, 1.30-2.76] and 1.53 [1.30-1.81] and 1.55 [1.03-2.33], respectively).

Abbreviations: BMD, bone mineral density; CI, confidence interval; RA, rheumatoid arthritis.

*Final patient attendance rate, 48.6%; control subjects, 59.8%. See “Results” section for details.†Odds ratio and/or 95% CI could not be presented because of distribution of data set; P < .02.

Our study is large and population based, and thus includes patients from the whole spectrum of disease severity and medication use. The design, including matched...
controls, strengthens the possibility that any differences between the patients and controls are consequences of RA. Furthermore, our results are fortified by the fact that all radiographs were evaluated according to 2 widely used and accepted methods of defining vertebral deformities.\textsuperscript{22,24} The overall prevalence of vertebral deformities was higher with the semiquantitative method, which is in accordance with previous findings.\textsuperscript{26} These were almost totally attributable to single, mild deformities in both patients with RA and controls. Some of these mild deformities might be due to other causes than osteoporosis, such as degenerative changes or Scheuermann disease.

The validity of our results depends on the representativeness of the included patients with RA compared with the underlying RA population, and on the control group compared with the underlying population in Oslo. Our group previously showed that the Oslo RA register comprises most of the patients with RA in the county.\textsuperscript{2} No obvious differences could be demonstrated in demographic, disease activity, disease severity, or health status measurements when patients with and without BMD were compared, except for a small difference in age. Thus, it is likely that patients examined in our study were representative of the underlying female RA population in the county for the current age group.

The control group was designed to match the RA population, and thus included subjects with various chronic diseases, as well as users of medications that influence BMD. The most striking difference between the patients and controls was a mean difference in weight of 3.4 kg. This difference is likely to reflect a real difference in patients and controls, as RA is associated with a higher prevalence of low body mass index than in the general population.\textsuperscript{27} The BMD values of controls were slightly higher than those in a previous, but smaller, population-based study from Oslo.\textsuperscript{28} We do not know whether this is due to an overestimation or underestimation in either of the studies, or to secular changes in population BMD. The last alternative could be due to the increased awareness of osteoporosis in the population during the past decade, including wider use of hormone therapy (Table 1). This could only be clarified by identifying the population who declined to attend. For ethical reasons, we were not able to contact the control subjects who did not accept the invitation to participate in this study.

We chose to include BMD at the hip in the multivariate analysis, as this measurement site correlated better with vertebral deformities in bivariate analysis than did BMD at the spine (results not shown), and because the difference between patients with RA and controls was more pronounced at the hip than at the spine (Tables 3 and 4). The results were, however, similar if BMD at the total hip was replaced with BMD at L2-L4.

The relationship between vertebral deformities and subsequent osteoporotic fractures has been examined in postmenopausal women. The Study of Osteoporotic Fractures,\textsuperscript{10} a prospective study of more than 9000 US women 65 years or older, demonstrated that the risk of developing further vertebral fractures as well as hip fractures is related to the number and severity of prevalent vertebral fractures. These results were recently confirmed in the European Prospective Osteoporosis Study,\textsuperscript{11} where the risk of hip fractures was 3-fold in patients with 1 deformity at baseline and 7-fold in patients with 2 or more deformities. We assume that patients with RA who have multiple and severe vertebral deformities have a risk of further osteoporotic fractures similar to that seen in postmenopausal women. Thus, our finding of a more pronounced difference between patients and controls regarding multiple or severe deformities than single or mild deformities (Table 2) has practical consequences, taking into account the advances in the therapy for osteoporosis in recent years. In addition, multiple or severe deformities are associated with increased mortality and reduced quality of life compared with single or mild deformities.\textsuperscript{4,7,10,11}

Apart from defining the prevalence, studies on vertebral deformities in RA and in corticosteroid-induced osteoporosis are conducted to clarify clinically important issues: first, whether the underlying disease contributes to fractures independently of corticosteroid use, and second, whether the relationship between BMD and vertebral deformities is comparable to that seen in postmenopausal osteoporosis.\textsuperscript{13-15,18} Research published so far has not been powered or designed to make any conclusions on both issues. Two previous studies comparing patients with RA and controls have shown that the BMD reduction is significantly reduced also in corticosteroid-naive patients.\textsuperscript{15,17} We now demonstrate that being diagnosed as having RA is related to vertebral deformities independently of BMD and corticosteroid use. This strongly indicates that disease factors in themselves contribute to an increased risk of the clinically important end point of osteoporosis, eg, fractures. This finding could

| Table 4. Frequency of Osteoporosis* in Patients With RA and Control Subjects |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                 | Patients, No. (%) | Controls, No. (%) | Odds Ratio 95% CI |
| Femoral neck                    | 42 (18.6)        | 14 (6.2)        | 4.11 2.00-9.69   |
| Total hip                       | 39 (17.3)        | 10 (4.4)        | 5.83 2.43-17.09  |
| L2-L4                           | 54 (22.0)        | 32 (13.1)       | 1.96 1.16-3.39   |
| Any measurement site            | 75 (30.6)        | 38 (15.5)       | 2.48 1.54-4.00   |

Abbreviations: CI, confidence interval; RA, rheumatoid arthritis.

*Defined as T-scores of −2.5 SDs or less.
have important implications for prevention of established osteoporosis in RA.

Our study confirms that patients with RA have significantly lower BMD than controls (Tables 3 and 4). This was especially apparent in patients with a history of long-term corticosteroid use. Corticosteroid use could serve as a marker for higher or long-standing disease activity, rather than being a risk factor in itself. The relative role of corticosteroids and inflammation as major pathogenic factors in bone loss in RA is a matter of controversy, but our study was not designed to clarify this issue. The results from the multivariate analysis indicate that BMD has a major influence on deformity prevalence in RA, but that the increase in vertebral deformities cannot be attributed to the BMD reduction alone.

The present study demonstrates a 2- to 3-fold increase in vertebral deformity prevalence in patients with RA compared with matched control subjects, and that this group seems to be especially prone to developing multiple or severe deformities. Longitudinal investigations are needed to clarify which patients with RA will develop vertebral deformities, and to determine whether long-term consequences of vertebral deformities seen in postmenopausal osteoporosis also apply to patients with osteoporosis caused by inflammatory diseases or corticosteroid use. Our findings suggest that RA in itself is a risk factor for developing vertebral deformities. Disease activity, dose of corticosteroids, and BMD should all be considered in the treatment of patients with RA to prevent osteoporotic fractures.

Accepted for publication March 21, 2003.

This study was supported in part by grants from the Research Council of Norway, Oslo; Lions Clubs International MD 104, Bergen, Norway; the Norwegian Rheumatism Association, Oslo; the Norwegian Women’s Public Health Association, Oslo; and the Norwegian Osteoporosis Foundation, Oslo. None of the sponsors took any part in the design of the study, analysis of results, or writing of the article.

We thank our research nurses, Margarette Svinsson, RN, Ingrid Müller, RN, Sidsel Arnhørrn, RN, and Anne Katrine Kongtorg, RN, for their expert technical assistance and medical students, Aasne Ask Hylßmo, Siri Seterelv, Pernelle Boyesen, and Mathilde Irgens, for their participation in data collection and processing.

Corresponding author and reprints: Ragnhild E. Ørstavik, MD, Department of Rheumatology, Diakonhjemmet Hospital, Box 23, Vinderen, N-0319 Oslo, Norway (e-mail: ragnhild.orstavik@ioks.uio.no).

REFERENCES