Vertebral Fracture Risk With Long-term Corticosteroid Therapy

Prevalence and Relation to Age, Bone Density, and Corticosteroid Use

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Background: Few data are available regarding vertebral fracture risk in patients treated with oral corticosteroids. The aim of this study was to determine the prevalence and the role of risk factors such as age, bone mineral density (BMD), and corticosteroid use for vertebral deformity in patients receiving long-term corticosteroid therapy.

Methods: Thoracolumbar x-ray films, BMD, and details on corticosteroid use were obtained on 229 consecutive patients treated with long-term corticosteroid regimens (≥6 months of prednisone, ≥5mg/d or equivalent) seen at 4 referral centers. Comparisons were made with a population control group of 286 male and female controls not taking corticosteroids (aged ≥60 years).

Results: Sixty-five patients (28%) had at least 1 vertebral deformity and 25 (11%) had 2 or more vertebral deformities. Older age, independent of BMD, was a significant risk factor for deformity. Patients aged 70 to 79 years had a 5-fold increased risk of deformity compared with patients younger than 60 years (odds ratio, 5.13; 95% confidence interval, 2.03-13.0). Compared with the population controls, the prevalence of deformities increased to a greater extent with each decade of age in the corticosteroid group (P = .005). Mean lumbar spine and femoral neck BMD Z scores were lower in the steroid-treated patients with deformities compared with the nonsteroid control group with deformities. When the effects of age, sex, body mass index, and duration of corticosteroid use were adjusted for in logistic regression analysis, low BMD was a modest predictor of deformity (for a 1-SD decrease in lumbar spine BMD: odds ratio, 1.31; 95% confidence interval, 1.02-1.68) and for a 1-SD decrease in femoral neck BMD: odds ratio, 1.77; 95% confidence interval, 1.07-2.94).

Conclusions: The combination of increasing age and corticosteroid use is associated with a marked increase in the risk of vertebral deformity. Elderly patients commencing long-term corticosteroid therapy should be considered for antiosteoporotic therapy independently of their BMD.

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Corticosteroids are effective and widely used as therapy for many chronic inflammatory and immune disorders. Indeed, a large cross-sectional study on patients of general practices in England found that 1 in 70 patients aged 55 years or older were taking continuous oral corticosteroid treatment for at least 3 months, with a median duration of treatment of 3 years. Osteoporosis is a widely recognized complication of corticosteroid therapy, and corticosteroid use is thought to increase the risk of osteoporotic fracture by accelerating bone loss in regions of the skeleton with high trabecular bone content such as the spine. However, there have been few and small studies on the prevalence of fracture in long-term steroid users.

The risk of fracture with corticosteroid use is thought to increase with higher doses and longer duration of therapy, but most studies have used bone mineral density (BMD) as their end point rather than fracture. It is also unclear whether the relation between BMD and fracture risk is the same in corticosteroid-treated patients as in postmenopausal women with osteoporosis. Moreover, the relative role of other risk factors for fracture (eg, age and sex) in long-term steroid users is unclear.

In this study, we report the results of a cross-sectional study on male and female long-term corticosteroid users in whom vertebral deformity and BMD were assessed. The aims of the study were to determine the prevalence of vertebral deformities and examine the role of risk factors such as age, steroid use duration, and
SUBJECTS AND METHODS

SUBJECTS

Subjects taking continuous long-term corticosteroids (defined as ≥6 months of prednisone, ≥5 mg/d or equivalent), aged 20 to 80 years, were recruited into the study between April and October 1998. They were from 2 sources: consecutive patients referred by rheumatologists for a clinical trial in corticosteroid osteoporosis (Sydney, New South Wales, and Geelong, Victoria) and consecutive patients attending a rheumatology outpatient service (Sunshine Coast, Queensland, and Hobart, Tasmania). Clinical details with regard to age, sex, underlying disease for which the corticosteroids were prescribed, estimated cumulative corticosteroid dose, current daily corticosteroid dose, duration of corticosteroid therapy, menopausal status, smoking history, and concomitant medications were recorded. Height was measured in meters and weight in kilograms. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

RADIOGRAPHIC ASSESSMENT

Lateral radiographs of the thoracic and lumbar spine (T4-L5 were graded independently by 1 of the investigators (V.N.) who was blinded to whether subjects were corticosteroid users or noncorticosteroid controls. Vertebral deformity was assessed semiquantitatively by a method similar to that described by Genant et al. and deformity was deemed to be present if there was more than a 20% reduction in anterior, middle, or posterior vertebral height. Relative vertebral heights are unaffected by differences in spine-film or film-focus distance,13 which allowed the use of x-ray films from different centers.

BMD MEASUREMENTS

Bone mineral density was measured at the lumbar spine (L2-L4) and the neck of the femur by dual energy x-ray absorptiometry using Lunar DPX-L scanners (LUNAR Corporation, Madison, Wis) in Geelong, Hobart, and Sunshine Coast and a Hologic scanner (Hologic 4500; Hologic Inc, Waltham, Mass) in Sydney. For comparison of patient data performed on the 2 different dual energy x-ray absorptiometry scanner types, the Hologic BMD values were converted to Lunar values using standardization formulas.

Patient BMD values were expressed as Z scores (age and sex matched) by comparison with a healthy population of male and female volunteers aged 20 to 80 years (n=400).

CONTROL COMPARISONS

Vertebral deformity prevalence in the subgroup of corticosteroid users aged 60 years or older was compared with prevalence in 286 male and female controls aged 60 years or older who were assessed concurrently in a population survey conducted by the investigators. In that survey, BMD was also measured and expressed as Z scores using the same reference values as described above. This allowed BMD fracture thresholds to be compared between the steroid-treated patients (age ≥60 years) and the control group.

STATISTICAL ANALYSIS

The prevalence of vertebral deformities was examined in the patient population as a whole and in several subgroups. Student t tests (for normally distributed variables) and a nonparametric test, Mann-Whitney U test (for variables not distributed normally), were used to determine statistically significant differences in variables between deformity and no-deformity groups. Potential risk factors for prevalence of vertebral deformity (age, sex, underlying disease, duration of disease, smoking status, menopausal status, steroid dose, steroid duration and estimated cumulative dose, and BMD) were first assessed in a univariate analysis. Potentially significant variables (P<.25 in the univariate model) and possible interaction terms were tested for significance in logistic regression models by backward elimination method to arrive at the model of best fit using a validated method. Significant variables and variables thought to be of biological importance (BMI, duration of steroid use, and BMD) were included in the final logistic regression model. The effects of study center, study source, underlying disease, concomitant medications (eg, hormone replacement therapy, calcium, bisphosphonates) and smoking history on the odds ratios and significance of the variables included in the final model were also examined. Fracture prevalence and BMD Z scores were compared between the steroid and control groups. To determine whether the influence of age on the prevalence of vertebral deformity was modified by steroid use, all subjects (steroid-treated patients and controls) were included in one logistic regression model and the significance of the interaction term of age and steroid use was examined. All analyses were performed using Statview 5.5 (SAS Institute, Cary, NC) statistical program.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

Demographic characteristics of the study population are shown in Table 1. Vertebral x-ray films were graded in 229 patients and BMD results were obtained in 194. More than 60% of the study group were older than 60 years and 69% were female. There was a wide range in the duration of disease (12-768 months) and duration of steroid treatment (6-445 months). The median duration of corticosteroid use was 4.8 years. There was also a diversity of underlying diseases for which the patients were taking corticosteroids. The majority of patients (62%) were referred from rheumatology outpatient services, while the rest were referred for the clinical trial.

PREVALENCE OF VERTEBRAL DEFORMITIES

At least 1 vertebral deformity was identified in 65 (28%) subjects (Table 2). Two or more fractures were pres-
ent in 25 (11%). The prevalence of deformity increased with age. Deformities were more common in men than women ($\chi^2=4.3, P<.05$). Interestingly, the subgroup classified as having “other rheumatic diseases,” such as systemic lupus erythematosus, ankylosing spondylitis, and polymyositis, had a much lower prevalence that was not explained by differences in age, steroid use, or BMD.

**COMPARING DEFORMITY GROUP VS NO-DEFORMITY GROUP**

Steroid users with at least 1 vertebral deformity were compared with the patients who had no deformities (Table 3). The group with vertebral deformities was significantly older and had a significantly longer duration of steroid use. Body mass index, duration of disease, current steroid use, and maximum steroid dose were not significantly different between the 2 groups. The mean BMD of spine and hip was lower in the deformity group.

**RISK FACTORS FOR VERTEBRAL DEFORMITY**

Risk factors for vertebral deformity are shown in Table 4. In multivariate logistic regression, 2 models were fitted that adjusted for age, BMI, duration of corticosteroid use, sex, and either lumbar spine BMD Z scores or femoral neck BMD Z scores. Age of 70 years and older was the strongest risk factor for the prevalence of vertebral deformity. There were only 8 patients 80 years or older, resulting in wide confidence intervals for this age category. Age was fitted as a categorical variable as it did not fit a linear logit pattern as a continuous variable. Age remained an independent risk factor when the raw BMD values rather than the Z scores were included in the model (data not shown).

Male sex was a significant factor in univariate analysis but not after adjusting for other risk factors. Increasing duration of corticosteroid use showed a nonsignificant trend, suggesting increased risk. Decreasing lumbar and femoral neck scores significantly increased risk of vertebral deformity. Including study center or patient source in the model made little difference to the odds ratios. Removing those who had taken calcium or ever smoked and adjusting for hormone replacement therapy use did not alter the odds ratios significantly. Although patients in the “other rheumatic diseases” group were at significantly lower risk of having vertebral deformities, when the data were analyzed by excluding these subjects from the logistic regression model, there was little difference to the results. The Pearson $\chi^2$ and deviance as a test of goodness of fit of the logistic regression model were high $P$ values, suggesting a good fit with the variables chosen for the final models.

**COMPARING STEROID-TREATED PATIENTS WITH HEALTHY CONTROLS**

In Figure 1, corticosteroid-treated patients aged 60 years and older are compared with healthy control subjects. The 2 populations did not differ significantly by age or sex distribution. Compared with the nonsteroid group, the prevalence of deformities increased to a greater extent with each decade of age in the corticosteroid group. Moreover, age X steroid use was a significant interaction term ($P=.005$) when patient and control data were pooled in the combined logistic regression model. This could not be explained by a longer duration of steroid use in older patients as there was no relation between age and duration of steroid use.

### Table 1. Demographic Details of 229 Corticosteroid-Treated Patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mean (SD) Value</th>
<th>No Deformity</th>
<th>Deformity (≥1)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.7 (11.6)</td>
<td>58.5 (12.5)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.0 (4.6)</td>
<td>26.3 (4.7)</td>
<td>.68</td>
<td></td>
</tr>
<tr>
<td>Duration of disease, mo</td>
<td>140 (133)</td>
<td>138 (132)</td>
<td>.561</td>
<td></td>
</tr>
<tr>
<td>Duration of steroid use, mo</td>
<td>91 (76)</td>
<td>74 (70)</td>
<td>.041</td>
<td></td>
</tr>
<tr>
<td>Maximum steroid dose, mg</td>
<td>47 (124)</td>
<td>42 (117)</td>
<td>.14†</td>
<td></td>
</tr>
<tr>
<td>Current steroid dose, mg</td>
<td>8.6 (9.1)</td>
<td>7.5 (5.2)</td>
<td>.51†</td>
<td></td>
</tr>
<tr>
<td>Lumbar BMD Z score</td>
<td>−0.84 (1.5)</td>
<td>−0.26 (1.7)</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Femoral neck BMD Z score</td>
<td>−0.92 (0.93)</td>
<td>−0.63 (0.94)</td>
<td>.06</td>
<td></td>
</tr>
</tbody>
</table>

*BMD indicates bone mineral density.
†Nonparametric test, Mann-Whitney U test.

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**COMPARING BMDs**

The mean BMD Z scores of the spine and femur were lower in the steroid users compared with the control group regardless of the presence or absence of vertebral deformities (Figure 2). This reached statistical significance at the lumbar spine in women (those with deformity, mean BMD Z scores –0.44 vs +0.58 [P = .01]; those with no deformity, mean BMD Z scores –0.01 vs +0.62 [P = .02]).

**COMMENT**

In this study, the prevalence of vertebral deformity in corticosteroid-treated patients was associated with age, increasing dramatically for each decade of age above 60 years. Moreover, in the multivariate analysis that included BMD (either Z score or raw value), age was the strongest independent predictor of deformity. The interaction between corticosteroid use and age was confirmed when comparisons were made with nonsteroid controls. This higher risk in elderly persons is consistent with 2 recent clinical trials of the prevention of corticosteroid-induced osteoporosis,17,18 which were able to show a significant decrease in vertebral fracture rate in the subgroup of older postmenopausal women, even though these studies were only powered to show differences in BMD.

The data suggest that decreased BMD alone does not account for the age-related increase in deformity prevalence. There are a number of possible explanations for this. Bone density measured by dual energy x-ray absorptiometry does not differentiate between cortical and trabecular bone. It may be that the older steroid-treated patients have lost a disproportionate amount of trabecular bone, leading to a greater loss of vertebral strength that is not entirely by BMD. The presence of spinal degenerative disease can also confound BMD measurements. Measuring vertebral bone mass by lateral spine densitometry19 or quantitative computed tomography20 may be a more sensitive indicator of corticosteroid-induced trabecular bone loss than measures by dual energy x-ray absorptiometry in the anteroposterior projection as commonly used. Age may be associated with qualitative changes in bone, leading to increased brittleness and microfractures that may be worsened by steroid therapy. Other influences related to age that might increase loading on vertebra include age-related intervertebral disk degeneration and weakening of abdominal and paravertebral musculature.21

Most previous studies of vertebral fracture associated with corticosteroid use have been smaller and compared fracture prevalence between steroid-treated patients and nonsteroid-treated patients but not with randomly selected healthy population controls as in this study. These studies have generally found a higher prevalence of vertebral fracture in the steroid-treated patients than nonsteroid-treated patients, but because healthy controls...
controls were not studied, the effect of the underlying disease on vertebral fracture prevalence was unclear.\textsuperscript{5,6,11,22-25} Peel et al,\textsuperscript{25} in a similar design to our study, also used healthy population controls. In their study, steroid-treated women with rheumatoid arthritis had a higher vertebral fracture prevalence, but the effect of age was only modest, possibly because the disease group were taking lower daily doses of corticosteroids (2.5 mg to 5 mg of prednisone) compared with our study (≥5 mg of prednisone), and the numbers studied were much smaller.

Although there were risk factors for fracture independent of BMD, the mean BMD Z scores of the spine and femoral neck were lower in the steroid group compared with the control group. Even when the groups without deformities were compared, BMD Z scores were lower in the steroid group, and these differences were significant at the spine in women. The difference in lumbar BMD in men may have been confounded by coexisting vertebral osteoarthritis.\textsuperscript{26}

It is difficult to know how much of the decreased BMD at both the spine and hip is a direct effect of corticosteroid use. Bone mineral density in corticosteroid users is also influenced by a complex interplay of a number of other factors, such as underlying disease, disease activity, and functional status.\textsuperscript{27,28} For example, a 2-fold increased risk of vertebral deformities in patients with active rheumatoid arthritis could not be attributed to the use of corticosteroids.\textsuperscript{29} In fact, the use of corticosteroids may reduce bone loss in some patients by suppressing disease activity and improving mobility.\textsuperscript{30} Parameters of disease activity or functional status were not measured in our study group, but adjustment for underlying disease per se did not alter the pattern of results.

Two recent studies have raised the possibility that vertebral fractures due to corticosteroids occur at a high BMD level than in other forms of osteoporosis. In a small group of steroid-treated patients with rheumatoid arthritis (n = 76), no significant difference was found in BMD between those with and without vertebral fractures,\textsuperscript{11} leading to suggestions that abnormal bone quality rather than BMD may explain the occurrence of vertebral fractures. However, in that study, mean lumbar spine and femoral neck BMD were lower (albeit not significantly) in patients with fracture, suggesting power issues may have been important. In another small study, BMD in steroid-dependent asthmatic patients with vertebral fractures was higher than in a group with recent nontraumatic vertebral fracture but not taking corticosteroids.\textsuperscript{7} This contrasts with the results of our study where BMD was lower in corticosteroid-treated patients with deformities than the steroid nonusers with deformities. When the 90th percentile of the mean BMD in the lumbar spine was chosen as the fracture threshold, analogous to the method used in the study described above,\textsuperscript{2} the fracture threshold was lower in our steroid group compared with the nonsteroid fracture group. This applied when the female and male data were analyzed separately. Thus, the results of the present study do not support the hypothesis of a higher BMD fracture threshold for steroid-treated patients. Corticosteroid bone loss appears to be dose related, and our deformity group had a longer mean duration of steroid use than the patients without deformities. However, we were unable to accurately estimate steroid dose in the present study.

Men had a higher prevalence of deformities, although when adjusted for age and BMD, sex was not a significant risk factor. The higher prevalence in older men may relate to greater occupational trauma in their previous working life. In the large European Vertebral Osteoporosis Study on vertebral deformities in healthy people, the prevalence of vertebral deformity was greater in younger men that in women,\textsuperscript{13} which was attributed to trauma. In the Dubbo Australian population study, the prevalence of vertebral deformity increased with age in both sexes, but prevalence was higher in men aged 60 to 64 years and women only overtook men in the older age group (age >80 years).\textsuperscript{15}

The use of a semiquantitative method to define vertebral deformity has been shown to be comparable to a number of morphometric methods.\textsuperscript{31} Vertebral “fractures” identified by radiological criteria are not necessarily associated with past or present symptoms, so it has been convention to use the term “deformity.” Vertebral deformities are clinically relevant as they have been shown to be associated with progressive kyphosis, loss of stature, and chronic pain\textsuperscript{12} as well as being a strong risk factor for incident fractures.\textsuperscript{33}

Our study has several limitations. Given the cross-sectional design of this study, it was not possible to control for all confounders. Factors such as severity of disease and functional disability vary during the course of the disease. The method used to define vertebral deformities may have been oversensitive and some nonclinically significant vertebral anomalies may have been graded as deformities. Comparison of prevalence rates with those in a healthy nonsteroid group using comparable methodology largely accounts for any differences in criteria. Even though this is one of the largest studies of long-term corticosteroid users, the nonsignificant trends for duration of steroid use in the multivariate model suggest that studies with even a larger group of patients needs to be undertaken. Finally, the findings of this study may not be generalizable to all persons taking corticosteroids, as a majority of our patients were from a rheumatic disease population. Similar studies need to be conducted on persons who are taking corticosteroids for other underlying diseases.

To summarize, we have shown that age is an independent risk factor for vertebral deformity in patients taking long-term corticosteroid therapy, with very high prevalence rates in those older than 70 years. Low BMD was associated with only a modest increase in fracture risk when adjusted for age and corticosteroid use, suggesting that factors other than decreasing BMD play a major role in increasing the risk of vertebral fracture. Increasing duration of corticosteroid use may also increase the risk of fracture. Large longitudinal studies are needed to know more about how BMD and corticosteroid dose influence the risk of fracture in patients who are taking long-term corticosteroids. Recent clinical trials have suggested prophylactic therapy can decrease fracture rate in older postmenopausal women starting corticosteroid therapy, and our results suggest these patients be considered for such therapy.
REFERENCES


