

## Bone Density Threshold and Other Predictors of Vertebral Fracture in Patients Receiving Oral Glucocorticoid Therapy

T. P. Van Staa,<sup>1</sup> R. F. Laan,<sup>2</sup> I. P. Barton,<sup>3</sup> S. Cohen,<sup>4</sup> D. M. Reid,<sup>5</sup> and C. Cooper<sup>6</sup>

**Objective.** To evaluate predictors of vertebral fractures, including a threshold for bone mineral density (BMD), in patients receiving oral glucocorticoids (GCs).

**Methods.** Data were obtained from 2 randomized clinical trials (prevention and treatment trials of risedronate) using similar methods, but different inclusion criteria were applied with regard to prior exposure to GCs. Predictors of vertebral fracture in the placebo group were identified using Cox regression with forward selection. The BMD threshold analysis involved a comparison of the 1-year fracture risk in postmenopausal women receiving placebo in the GC trials with that in postmenopausal women not taking GCs in 3 other trials.

**Results.** The study population comprised 306 patients with baseline and 1-year followup data on vertebral fractures (111 receiving placebo and 195 receiving risedronate). In the placebo group, the statistically significant predictors of incident fracture were the baseline lumbar spine BMD (for each 1-point decrease in T score, relative risk [RR] 1.85, 95% confidence interval [95% CI] 1.06–3.21) and the daily GC dose (for each 10-mg dose increase, RR 1.62, 95% CI 1.11–2.36). In the BMD threshold analysis, compared with nonusers of GCs, patients receiving GCs were younger, had a

higher BMD at baseline, and had fewer prevalent fractures; nevertheless, the risk of fracture was higher in the GC users compared with nonusers (adjusted RR 5.67, 95% CI 2.57–12.54). The increased risk of fracture was observed in GC users regardless of whether osteoporosis was present.

**Conclusion.** The daily, but not cumulative, GC dose was found to be a strong predictor of vertebral fracture in patients receiving GCs. At similar levels of BMD, postmenopausal women taking GCs, as compared with nonusers of GCs, had considerably higher risks of fracture.

Oral glucocorticoids (GCs), also known as oral corticosteroids, are widely used for the treatment of a variety of inflammatory and allergic disorders. Estimates in the US suggest that 1–3% of men and women over age 50 years are receiving long-term GC therapy (1). Data from the UK also report frequent use of GC therapy in the elderly (2). It is now well recognized that treatment with GCs can lead to rapid loss of bone mineral density (BMD) and to an increased risk of fracture (3). Several epidemiologic studies have reported a doubling of the risk of hip fracture in GC users (4–6). In the largest of these studies, a rapid increase in fracture risk following the start of GC therapy and a strong correlation of risk with daily GC dose were found (6,7). Two smaller studies demonstrated that the cumulative (compared with daily) GC dose was the stronger predictor of fracture (8,9).

Fractures in GC users may occur as a consequence of bone loss; however, there is increasing interest in the possible role of microarchitectural change in GC-induced fractures. Recently, the hypothesis was proposed that osteocyte apoptosis could lead to a deterioration of bone quality, with rapid increases in the risk of fracture (10). Consistent with the notion of a non-BMD-related mechanism being responsible for inducing

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<sup>1</sup>T. P. van Staa, MA, MSc, MD, PhD: University of Southampton, Southampton, UK, Procter & Gamble Pharmaceuticals, Egham, UK, and Utrecht University, Utrecht, The Netherlands; <sup>2</sup>R. F. Laan, MD, PhD: University Medical Centre, Nijmegen, The Netherlands; <sup>3</sup>I. P. Barton, BSc: Procter & Gamble Pharmaceuticals, Egham, UK; <sup>4</sup>S. Cohen, MD: St. Paul Medical Center, Dallas, Texas; <sup>5</sup>D. M. Reid, MD, FRCP: University of Aberdeen, Aberdeen, UK; <sup>6</sup>C. Cooper, MA, DM, FRCP, FmedSci: University of Southampton, Southampton, UK.

Address correspondence and reprint requests to R.F. Laan, MD, PhD, Professor of Rheumatology, University Medical Centre, Geert Grooteplein Zuid 8, Nijmegen 6500 HB, The Netherlands.

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fractures, Luengo et al observed that GC users with a fracture had considerably higher BMD than did patients with involuntional osteoporosis and fracture (11). However, this observation was not confirmed in a second observational study (12).

Accordingly, we used data from the placebo arms of 2 large randomized, controlled trials of risedronate, to evaluate the predictors of vertebral fracture in GC users. In addition, we determined the BMD threshold for vertebral fracture by comparing postmenopausal GC users with postmenopausal GC nonusers.

## PATIENTS AND METHODS

**Study population of GC users.** The study was based on data from 2 randomized, double-masked, placebo-controlled trials of risedronate therapy conducted among patients with a variety of rheumatic, pulmonary, and skin disorders. The design of these 1-year studies has been described elsewhere (13,14). Ambulatory men and women, ages 18–85 years, were enrolled. The first study (referred to as the treatment study) was performed in patients who had been receiving oral GC therapy (mean daily dose  $\geq 7.5$  mg of prednisone or equivalent) for at least 6 months (14). The second study (prevention study) included patients who had begun taking moderate to high doses of oral GCs (mean daily dose  $\geq 7.5$  mg of prednisone or equivalent) within the 3 months prior to the start of the study (13). Inclusion of patients in these studies was not based on the BMD at baseline. The patients in each study were randomly assigned to receive either a 2.5-mg or 5.0-mg tablet of risedronate daily or an identical-appearing placebo tablet. All patients in the treatment study received 1 gm calcium and 400 IU vitamin D daily. In the prevention study, the calcium supplementation was lower (500 mg calcium) and vitamin D supplementation was recommended only in patients who had low baseline levels of this vitamin.

Patients were followed up for 1 year and assessed for changes in BMD of the lumbar spine and femoral neck, as well as for the incidence of vertebral fractures. Information on BMD and incidence of vertebral fracture was collected using similar methods in both studies. BMD at the lumbar spine and femoral neck was measured by dual-energy x-ray absorptiometry. Femoral neck BMD measurements were converted to the Third National Health and Nutrition Examination Survey index. Quantitative morphometry was used to identify prevalent (baseline) and incident (new) vertebral fractures. An incident vertebral fracture was defined as a decrease of  $\geq 15\%$  in vertebral height in a previously intact vertebra or as a reduction of  $\geq 4$  mm in previously fractured vertebrae. All incident vertebral fractures identified by morphometry were verified visually by a skeletal radiologist, who either confirmed or disqualified the fracture (13,14).

The study population consisted of all patients who underwent an assessment of vertebral fracture at baseline and during followup. The clinical predictors of incident vertebral fracture were evaluated in the placebo groups of the prevention and treatment studies. These predictors included age, sex, baseline lumbar spine and femoral neck BMD (T scores),

number of prevalent fractures, smoking history, body mass index, and daily and cumulative GC dose. The daily dose of GCs was based on the GC dose used at the start of the study. The cumulative dose included the total duration (in days) of prior GC therapy. The physician treating the patient's underlying disease determined the information on GC dose in the treatment study.

The statistical significance of each predictor ( $P < 0.05$ ) was identified using forward selection in a Cox proportional hazards regression model. For the statistically significant predictors, the relative risk (RR) of incident vertebral fracture in the risedronate group (2.5 mg or 5 mg) compared with the placebo group was estimated. In order to assess whether the risk reductions in the risedronate group were statistically comparable across these predictors, interaction terms between treatment and predictor were added to the Cox regression model.

**Comparison of GC users with nonusers.** The 1-year fracture rate in postmenopausal women who were receiving placebo in the GC trials was compared with that in postmenopausal women who were receiving placebo but not GCs in 3 other trials. These 3 trials comprised a study evaluating the effects of risedronate on hip fracture in elderly women and 2 studies evaluating the risk of vertebral fracture in women with established postmenopausal osteoporosis. The designs of these studies have been described elsewhere (15–17). Patients in these studies who had received any systemic GC in the year before baseline of the present study or at any time during each study were excluded from the analysis.

The analysis included all postmenopausal women with paired, evaluable thoracolumbar radiographs (at baseline and month 12). Two methods were used to identify potential vertebral fractures among the nonusers of GCs: a quantitative method (using criteria identical to those used in the 2 GC studies) and a semiquantitative method (based on the Genant scoring system) (18). An independent skeletal radiologist adjudicated any differences between the methods. In the GC users, only the quantitative method with adjudication was used for vertebral fracture assessment. Among the 129 nonusers of GCs who had an incident vertebral fracture at the end of the 1-year followup, there were 6 patients (4.7%) who had incident vertebral fractures that were identified by the semiquantitative method, but not by the quantitative method.

The relationship between baseline BMD and incidence rates of vertebral fractures was estimated in both GC users and GC nonusers. For each group, the observed range of baseline BMD was divided into 5 equal subgroups (based on quintiles of BMD). The Kaplan-Meier incidence of fracture was then estimated for each of these subgroups, followed by a smoothing of the individual estimates (19). This method, also known as spline regression, has been advocated as an alternative to categorical analysis (20).

## RESULTS

**Predictors of vertebral fracture in the study population of GC users.** Three hundred six patients who had an assessment of vertebral fracture at baseline and during followup were included in the study. The charac-

**Table 1.** Baseline characteristics of the 306 patients included in the study (i.e., those with vertebral fracture assessment)\*

Characteristic	Placebo (n = 111)	Risedronate (n = 195)
Age, mean $\pm$ SEM years	57.1 $\pm$ 1.3	59.6 $\pm$ 1.0
Men, no. (%)	38 (34.2)	58 (29.7)
Women, no. (%)	73 (65.8)	137 (70.3)
Premenopausal	17 (15.3)	26 (13.3)
Postmenopausal	56 (50.5)	111 (56.9)
Femoral neck, mean $\pm$ SEM T score†	-1.3 $\pm$ 0.1	-1.2 $\pm$ 0.1
Lumbar spine, mean $\pm$ SEM T score†	-1.4 $\pm$ 0.2	-1.2 $\pm$ 0.1
Prevalent vertebral fractures, no. (%) of patients		
None	72 (64.9)	138 (70.8)
$\geq 1$	39 (35.1)	57 (29.2)
Daily dose of prednisone or equivalent at baseline, mg		
Mean $\pm$ SEM	17.5 $\pm$ 1.4	16.6 $\pm$ 1.1
Median	11.3	10
Duration of glucocorticoid treatment at baseline, months		
Mean $\pm$ SEM	40.4 $\pm$ 6.7	31.1 $\pm$ 3.4
Median	8.6	9.0

\* One hundred seventy-four patients were enrolled in the treatment study (59 placebo and 115 risedronate) and 132 in the prevention study (52 placebo and 80 risedronate) (see refs 13 and 14, respectively).

† Data were missing on baseline lumbar spine bone mineral density (BMD) for 36 patients and on femoral neck BMD for 6 patients.

teristics of these patients are presented in Table 1. There were no statistically significant differences in age, sex, baseline BMD, and GC exposure between the placebo- and risedronate-treated patients. There were 30 patients who experienced an incident vertebral fracture during the 1-year period of observation. The incidence rate of vertebral fracture was 16.5% in the placebo group and 6.2% in the risedronate group. One-year vertebral fracture incidence rates were similar among the placebo patients in the prevention and treatment studies.

Table 2 shows the 2 predictors of incident vertebral fracture in the placebo group that were identified by

**Table 2.** Predictors of incident vertebral fracture in the placebo group\*

Predictor	Relative risk (95% confidence interval)
Baseline lumbar spine BMD	1.85 (1.06–3.21)†
Daily GC dose	1.62 (1.11–2.36)‡

\* Predictors were determined on the basis of forward selection in a Cox proportional regression model of the following variables: age, sex, baseline lumbar spine and femoral neck bone mineral density (BMD), number of prevalent fractures, smoking history, body mass index, and cumulative and daily glucocorticoid (GC; prednisone or equivalent) dose.

† For each 1-point decrease in T score.

‡ For each increase of 10 mg/day.

forward logistic regression as statistically significant: baseline lumbar spine BMD and daily GC dose. Backward selection analysis yielded results similar to those obtained by forward selection. Given the possible correlation between baseline lumbar spine BMD and baseline femoral neck BMD, models were constructed with inclusion of baseline BMD at only one of these sites. With inclusion of baseline femoral neck BMD, the statistically significant predictors of incident fracture were the number of prevalent fractures and the daily GC dose. The cumulative GC dose did not predict the occurrence of fracture in either model tested.

Table 3 shows the reduction in risk of incident vertebral fracture in the risedronate group (relative to the placebo group) across the distributions of baseline lumbar spine BMD and daily GC dose. Reductions in risk were similar irrespective of the BMD T score or daily GC dose (test for interaction  $P > 0.05$ ).

**Fracture risk in postmenopausal GC users compared with GC nonusers.** In the BMD threshold analysis, the 1-year fracture risk in 56 postmenopausal women receiving placebo in the GC trials was compared with that in 1,899 postmenopausal women who were not taking GCs. Compared with the nonusers, the GC users were, on average, younger (64.7 years versus 74.1 years), had higher baseline lumbar spine BMD (T score of -1.8 versus -2.6), had higher baseline femoral neck BMD (T score -1.9 versus -2.6), and had fewer prevalent vertebral fractures (42.9% versus 58.3%). Nevertheless, GC users had a higher incidence of new vertebral fractures (16.1%) than did nonusers (7.0%) (crude RR 2.48, 95% confidence interval [95% CI] 1.20–5.12). When adjusted for age, baseline BMD, number of prevalent vertebral fractures, height, and weight, the rate of fracture was increased almost 6-fold in the GC users as compared with the nonusers (adjusted RR 5.67, 95% CI 2.57–12.54). The difference between the crude and adjusted RRs may be explained by the large differences in baseline characteristics between the GC users and nonusers.

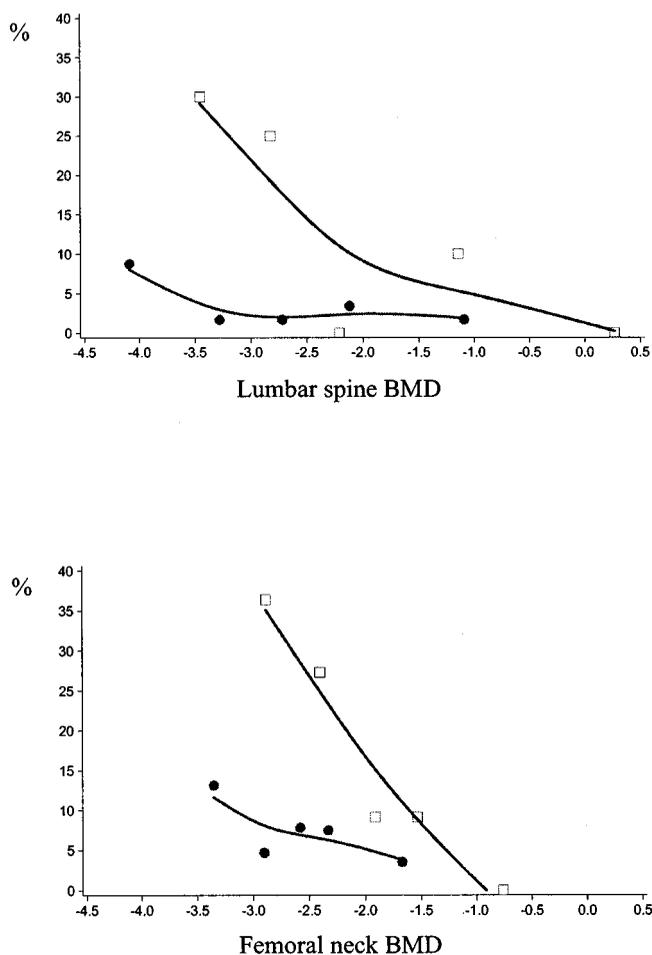
Baseline BMD was a determinant of incident vertebral fracture in both GC users and nonusers. However, fracture incidence was considerably higher in the GC users at any given level of BMD (Figure 1).

Additional analyses were conducted to evaluate the robustness of these results. A logistic regression model comparing the risk of fracture in GC users with that in nonusers yielded results comparable with those obtained in the risk analyses. Moreover, comparable results were obtained using a Cochran–Mantel–Haenszel test in the evaluation of efficacy of risedronate.

**Table 3.** Incidence of vertebral fractures (cases) in the risedronate and placebo groups, stratified by predictors of fracture\*

Predictor	Placebo		Risedronate		Relative risk (95% confidence interval)
	No. of cases	Incidence, %	No. of cases	Incidence, %	
Overall	18	16.5	12	6.2	0.34 (0.16–0.73)
Baseline lumbar spine BMD					
T score < - 2.5	8	34.8	6	15.0	0.34 (0.10–1.14)
T score ≥ - 2.5	4	5.9	3	2.2	0.40 (0.09–1.84)
Daily GC dose (prednisone or equivalent)					
≤15 mg/day	9	12.3	7	5.4	0.40 (0.14–1.13)
>15 mg/day	9	25.0	5	7.8	0.26 (0.08–0.84)

\* See Table 2 for definitions.



**Figure 1.** Incidence of vertebral fracture in patients receiving glucocorticoids (GCs) (□) compared with nonusers of GCs (●), by baseline lumbar spine bone mineral density (BMD) and femoral neck BMD. The individual data points correspond to the incidence in subgroups of the GC user and nonuser populations, as based on quintiles of baseline BMD. The solid line is a curve representing smoothing of these individual estimates.

### DISCUSSION

We have utilized data from 2 large, prospective, randomized, controlled trials to show that the daily GC dose, and not the cumulative dose, is a strong predictor of the risk of vertebral fracture. We have also demonstrated that postmenopausal GC users have considerably higher fracture risks than do nonusers of GCs, at similar baseline levels of BMD.

This study is the first prospective study to evaluate the incidence of fractures in patients on GC therapy, and clarifies whether the risk increase is related to the daily dose (rapid onset) or the cumulative dose (long-term effect) of GCs. Our findings are consistent with those of a large, retrospective epidemiologic study, which reported that the risk of nonvertebral fractures was increased by 54% in the first year of GC treatment (with daily doses >7.5 mg of prednisolone) (3,6). The risk of fracture was primarily related to the daily dose and not the cumulative dose (7). These findings support the notion that fractures can occur rapidly in patients receiving GC therapy.

We found that the BMD threshold for fracture was different in (postmenopausal) GC users compared with nonusers. This issue is controversial, and published data are inconsistent. Two studies have shown that the distribution of BMD among cases of vertebral fracture was similar between GC users and nonusers (12,21). The main limitation of these previous analyses is their reliance on prevalent fracture; BMD in patients with prevalent fractures is related not only to the underlying incidence rate of fracture, but also to the duration of therapy or disease (3). Therefore, the BMD of patients with incident fractures will be very different from that of patients with prevalent fractures. We believe it is inappropriate to make inferences on the BMD threshold for

new fractures on the basis of prevalent cases only. Furthermore, in the study by Selby et al, both the prevalence and severity of vertebral fracture were considerably higher in GC users compared with nonusers, despite the apparently similar levels of BMD (12).

Other studies support our observations that GC therapy influences fracture risk by a mechanism independent of BMD (3,11,22,23). One such mechanism for the rapid onset of fracture risk could be osteocyte apoptosis, leading to a deterioration of bone quality and early increases in fracture risk (10). Osteocyte apoptosis is prevalent in GC-induced osteoporosis (24), and preliminary results of an animal study demonstrated that osteocyte viability was an important determinant of bone strength independent of BMD (25). The network of osteocytes probably participates in the detection of microdamage and the transmission of signals that lead to bone repair by remodeling. Osteocyte apoptosis could compromise this mechanism, leading to microdamage accumulation and increased bone fragility (24). The adverse effects of GC therapy on the formation of osteoblasts (24) could further reduce this repair of microdamage.

Guidelines have been developed to establish intervention thresholds in GC-induced osteoporosis. The recent guidelines of the American College of Rheumatology advocate intervention in all patients who start GC therapy at  $\geq 5$  mg/day and in those patients on a long-term regimen of GCs with a BMD below a T score of  $-1.0$  (26). Guidelines from the UK advocate an intervention threshold at a T score of  $-1.5$  (27). The results of this study support the use of a higher BMD threshold in patients receiving GC therapy, since the postmenopausal women receiving GCs had considerably higher risks of fracture than did the GC nonusers at similar levels of BMD. There are, however, insufficient data in our study to establish whether a threshold of  $-1.0$  would be clearly preferable to that of  $-1.5$ .

Our study has several limitations. One is the small size of the population of GC users, which restricted our ability to identify all risk factors for fracture and could lead to statistically significant, but imprecise, estimates of fracture risk. A second limitation is that we did not adjust for disease severity in the comparison of GC users and nonusers. This is particularly relevant in drawing conclusions about the etiology of the increased risk of fracture in GC users. BMD measurements are primarily used to identify patients at high risk for fracture, irrespective of the underlying etiology of the reduced BMD. This study addressed whether BMD

measurements predicted fracture in a comparable manner between GC users and nonusers.

In the BMD threshold analysis, the vertebral fracture classification of nonusers was based on both a quantitative and a semiquantitative classification method, whereas that of GC users was based on a quantitative classification only. However, a radiologist visually adjudicated any differences in classification between the quantitative and semiquantitative methods among nonusers. We found that almost all verified vertebral fractures in the nonusers were identified by both the quantitative and semiquantitative method. A study comparing the reproducibility of different definitions of vertebral deformity also reported good concordance between these methods if used in combination with a visual assessment (28). Any bias due to the use of an additional method in identifying potential fractures in nonusers would have resulted in an overestimate of fracture incidence in the nonusers and an underestimate of the risk of fracture in GC users.

In conclusion, this study demonstrates that the risk of vertebral fracture increases rapidly in patients starting GC therapy. Our findings support the hypothesis that treatment with GCs influences the occurrence of fracture by a mechanism independent of BMD. Consequently, different BMD-intervention thresholds should be utilized in patients undergoing GC therapy.

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