Osteoporos Int (2002) 13:777–787

Osteoporosis International

Review Article

The Epidemiology of Corticosteroid-Induced Osteoporosis: a Meta-analysis

T. P. van Staa[1-3], H. G. M. Leufkens[2] and C. Cooper[1]

[1]MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, UK; [2]Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht, The Netherlands; [3]Procter & Gamble Pharmaceuticals, Staines, UK

Abstract. Studies of oral corticosteroid dose and loss of bone mineral density have reported inconsistent results. In this meta-analysis, we used information from 66 papers on bone density and 23 papers on fractures to examine the effects of oral corticosteroids on bone mineral density and risk of fracture. Strong correlations were found between cumulative dose and loss of bone mineral density and between daily dose and risk of fracture. The risk of fracture was found to increase rapidly after the start of oral corticosteroid therapy (within 3 to 6 months) and decrease after stopping therapy. The risk remained independent of underlying disease, age and gender. We conclude that oral corticosteroid treatment using more than 5 mg (of prednisolone or equivalent) daily leads to a reduction in bone mineral density and a rapid increase in the risk of fracture during the treatment period. Early use of preventive measures against corticosteroid-induced osteoporosis is recommended.

Keywords: Bone; Bone density; Fracture; Glucocorticoids; Iatrogenic disease; Meta-analysis; Review

Introduction

Corticosteroid-induced osteoporosis was discovered more than 60 years ago when Cushing first described the tendency of patients with excess endogenous corticosteroid to develop bone fractures [1]. But the relevance of these findings to exogenous oral corticosteroids (CS) has remained controversial for some time. A 1984 'evidence-based' review came to the conclusion that there was no 'evidence' to substantiate a causal role for corticosteroid therapy in producing clinically important osteoporosis [2]. However, expert opinion at that time, graded lower in the evidence hierarchy of meta-analysts, considered osteoporosis and vertebral compression fractures to be frequent serious complications of therapy [3]. More recently, the importance of corticosteroid-induced osteoporosis has become widely recognized and guidelines for its prevention and therapy have now been developed [4,5]. This article considers what is known about the epidemiology of corticosteroid-induced bone loss and fractures, providing a thorough review of the information on the predictors of bone loss and fractures.

Correspondence and offprint requests to: Professor Cyrus Cooper, MA DM FRCP, Professor of Rheumatology, MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, UK. Tel: +44 (0)23 8077 7624. Fax: +44 (0)23 8070 4021. e-mail: cc@mrc.soton.ac.uk

Methodology

Bibliographic reviews and literature searches of Medline and Embase were conducted to find peer-reviewed articles in English, German, French, Dutch or Spanish with data on the bone mineral density (BMD), bone mineral content or fracture rates of CS-treated patients.

BMD studies published over the last 20 years were classified either as cross-sectional or longitudinal studies. Cross-sectional studies were selected if average BMD values were provided for CS users and a control group. The percentage of normal was the ratio of average BMD value in the CS users to that of the control group.

Studies that provided *Z*-scores of CS users were also included. The average *Z*-score of the CS users was converted into the percentage of normal using published reference data [6–8]. For each age and sex group, the percentage of normal for a *Z*-score of 1 was estimated by dividing the standard deviation to the mean BMD value. The reference data corresponding to the mean age and sex of the CS users were used to calculate the percentage of normal from the average *Z*-score. Longitudinal BMD studies were analyzed separately and selected if they included only first-time CS users and provided data on the BMD changes at different times of follow-up.

The meta-analysis focused on the BMD measurements of lumbar spine, hip (femoral neck, total hip, trochanter, or Ward's triangle), distal and mid-shaft radius. The method of BMD measurement was noted (i.e., single photon absorptiometry, dual photon absorptiometry, quantitative computer tomography (QCT), or dual X-ray absorptiometry (DXA)) along with the average daily and cumulative CS dose. The cumulative dose, if not provided, was calculated from the daily dose and duration of use. Pearson correlation coefficients were calculated to assess the linear association between dose and BMD. Multiple linear regression analysis was used to evaluate the relationship between daily or cumulative CS dose and the percentage of expected BMD value. Each study was weighed according to the number of CS users. Analyses were adjusted for the mean age, percentage of women, indication for therapy, and method of BMD measurement.

Studies that provided information on the number of patients with a fracture in both CS users and a control group were also reviewed. The crude odds ratio of fracture was estimated for each study. The across-study odds ratio of fracture was estimated by combining the individual study estimates using the Mantel–Haenszel method. It was tested whether the study estimates were statistically similar (homogenous). Combined odds ratio may not be valid unless odds ratios are homogenous across studies.

Results of Review

Our review included 66 studies with BMD measurements in 2891 CS users [9–74]. Of these studies, most (56 studies with 2631 users) were cross-sectional whereas some (10 studies) followed 260 first-time CS users longitudinally [9,20,25,33,38,42,51,56,67, 71]. A majority of studies (66.7%) included less than 50 CS users and only four studies included a minimum of 100 users. Females were more often studied (71.5%) than men and the average age of study patients was 55.2 years. The most frequently cited indications for therapy were musculoskeletal disorders (67.1% of patients), followed by obstructive pulmonary disease (15.7%). Overall, the average daily dose was 9.6 mg of prednisolone (or equivalent), with a cumulative dose of 17.8 g and duration of use of 5.4 years. BMD was assessed using dual X-ray absorptiometry in 41 studies, single or dual photon absorptiometry in 25 studies, and quantitative computer tomography in seven studies.

The largest report which evaluated fractures was a population-based cohort study which included 244 235 CS users. This study (referred to as the General Practice Research Database (GPRD) study) was conducted in a general practice setting in the UK [75–79]. There were a further 29 smaller studies which have also investigated fracture [16,22,30,38,41,52,57,58,68,74,80–98]. Six studies were excluded from the analysis due to insufficient information for OR calculation [41,52,80,83,90,96]. The remaining 23 studies reported on 119 hip, 220 vertebral, 28 radius fractures and 191 fractures of unspecified locations in CS users. The average daily dose of CS used in these studies was 7.8 mg prednisolone and cumulative dose was 13.9 g prednisolone. These studies were analyzed separately from the GPRD study, given its much larger size.

Overall Skeletal Effects

A review of the studies that provided details on fractures showed that almost all reported higher rates of fracture in CS users, although this increase did not always reach statistical significance in the smaller studies. One cross-sectional study reported protective effects of CS for fracture [80]. As shown in Table 1, the relative rate (RR) of fracture in CS users was 1.33 (95% CI 1.29–1.38) in the GPRD study and 1.91 (95% CI 1.68–2.15) in all other studies. The risk of hip fractures was increased by 61% (RR=1.61; 95% CI 1.47–1.76) in the GPRD study and by 101% (RR=2.01; 95% CI 1.74–2.29) in all other studies. The RR for vertebral fractures was 2.60 (95% CI 2.31–2.92) and 2.86 (95% CI 2.56–3.16), respectively.

Lumbar spine and hip BMD measurements of CS users were consistently lower than that expected for a group of similar age and sex. Spine BMD was, on average, 89.4% of that expected (2305 users, 50 studies). For the hip, this figure was 88.8% (1955 users, 37

Table 1. RR of fracture in CS users in GPRD and other fracture studies

	GPRD [75] RR (95% CI)	Other studies[a] RR (95% CI)
Any fracture	1.33 (1.29–1.38)	1.91 (1.68–2.15)
Hip	1.61 (1.47–1.76)	2.01 (1.74–2.29)
Vertebral	2.60 (2.31–2.92)	2.86[b] (2.56–3.16)
Forearm	1.09 (1.01–1.17)	1.13 (0.66–1.59)

[a]References any fracture [16,22,74,86,88,93,97,98]; hip [30,74,81, 82,84–86,88,91,92,95,97]; vertebral [38,57,58,68,74,86–89,94,97,98]; forearm [85,88,97].
[b]Test for heterogeneity statistically significant (p value <0.05). Combined estimate may not be valid as individual studies had different results.

studies). The distal radius BMD was 88.3% of the expected value (591 users, 15 studies) and the mid-shaft 92.2% of the expected value (274 users, 8 studies). When the analysis was limited to studies that used dual X-ray absorptiometry, BMD was 90.8% of normal, 88.5% of that expected for the hip, and 97.8% of the value expected for the distal radius.

The adverse effects of CS therapy on bone were confirmed in two randomized controlled studies. The loss of lumbar spine BMD at 3 to 5 months was statistically significantly greater in patients using on average 7.5 mg prednisolone per day compared to randomly selected controls [38,51].

The ratio of trabecular bone relative to cortical bone can vary across sites in the body. The lumbar spine has the most trabecular bone, followed by the hip and distal radius. The mid-shaft radius consists primarily of cortical bone. Using QCT, it is possible to measure both trabecular and cortical BMD independently at one site. Of five recent studies that used this technique, the three larger studies reported statistically significant reductions of cortical BMD [39,95,99]. Two smaller studies reported only small reductions of cortical BMD in CS users [38,100]. In all but one study [39], the bone loss was found to be greatest in trabecular bone. One study reported that the cortical BMD was reduced in CS users and that the number of vertebral fractures per patient correlated highly with cortical BMD [95].

Relationship to CS Dose

The GPRD study found a strong relationship between daily dose and risk of fracture (Fig. 1). Excess fracture risk in CS users was stable at about 20% for daily doses lower than 5 mg prednisolone but increased for higher doses. Patients who used a daily dose of 20 mg had a non-vertebral fracture rate, which was about 60% higher than the rate in the control group [76]. Cumulative CS dose was also correlated to the risk of fracture, but this correlation was weaker than that observed between daily dose and risk of fracture. Positive correlations between cumulative dose and fracture risk were also found in other studies [89,97,101]. Two of these studies also evaluated the effects of daily dose and reported that cumulative dose was the stronger predictor of fracture [97,101]. In the meta-analysis of the other fracture studies, CS use was associated with an increased risk of fracture but there were no statistically significant correlations with either daily or cumulative dose.

A strong correlation was found between cumulative CS dose and decreases in spine and hip BMD (Fig. 2). The strong associations of spine and hip BMD with cumulative dose persisted when any study was excluded from the analysis. Regression analyses including both cumulative dose and the square of cumulative dose showed no evidence of non-linearity in the dose–response relation. Individual studies reported inconsistent results. A positive correlation with cumulative CS dose was reported in some, but not all, studies (positive correlation: references 11,21,26,28,31,35,40,50,56,59, 61,64,73,101; no correlation: references 14,22–24, 29, 33,37,41,43,45,46,62,65,66,102,103). In most of these studies, the statistical power to detect meaningful differences was not provided and was probably not large.

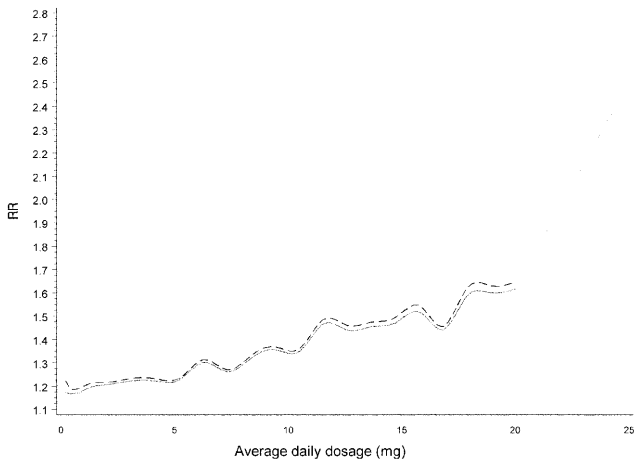

Fig. 1. Adjusted relative risk (RR) of non-vertebral fracture (and 95% confidence interval) stratified by daily dose in the GPRD study (adapted from van Staa et al [76], with permission).

The across-study evaluation did not find a statistically significant relationship between daily CS dose and decreases in BMD. After adjustment for cumulative dose and other variables, daily dose was not associated with BMD at any of those sites. Similar to the reports on cumulative dose, daily CS dose was found to be a predictor of BMD in some [15,35,103–104] but not in other studies [14,22–24,29,37,43,46,59,65,66,101].

It has been widely debated in the literature whether there is a dose threshold for the adverse bone effects of CS therapy. Studies of patients using daily doses on average of 7.5 mg prednisolone or lower at the time of BMD measurement found conflicting results. Several studies found no substantive reductions in BMD at lower doses [15,16,18,26,28,37,39,54–57,102,103], in contrast to others [29,30,36,43,47,68,98,105]. Interpretation of these results is complicated because the daily doses used prior to the BMD measurement were frequently unknown and not taken into account. More convincing information of the effects of low CS doses comes from two randomized clinical trials, which found statistically significant BMD reductions in patients using daily doses of 7.5 mg prednisolone: spine BMD loss of 8.2% at 20 weeks [38] and 2.0% at 12 weeks [51].

Onset of Skeletal Effects

Rapid onset of fracture was observed in the GPRD study [75]. Figure 3 shows the incidence of non-vertebral and vertebral fractures after starting CS therapy. In patients using 7.5 mg, or more, prednisolone per day, the risk of non-vertebral fractures was increased by 54% in the first year of therapy compared to baseline (unadjusted). In

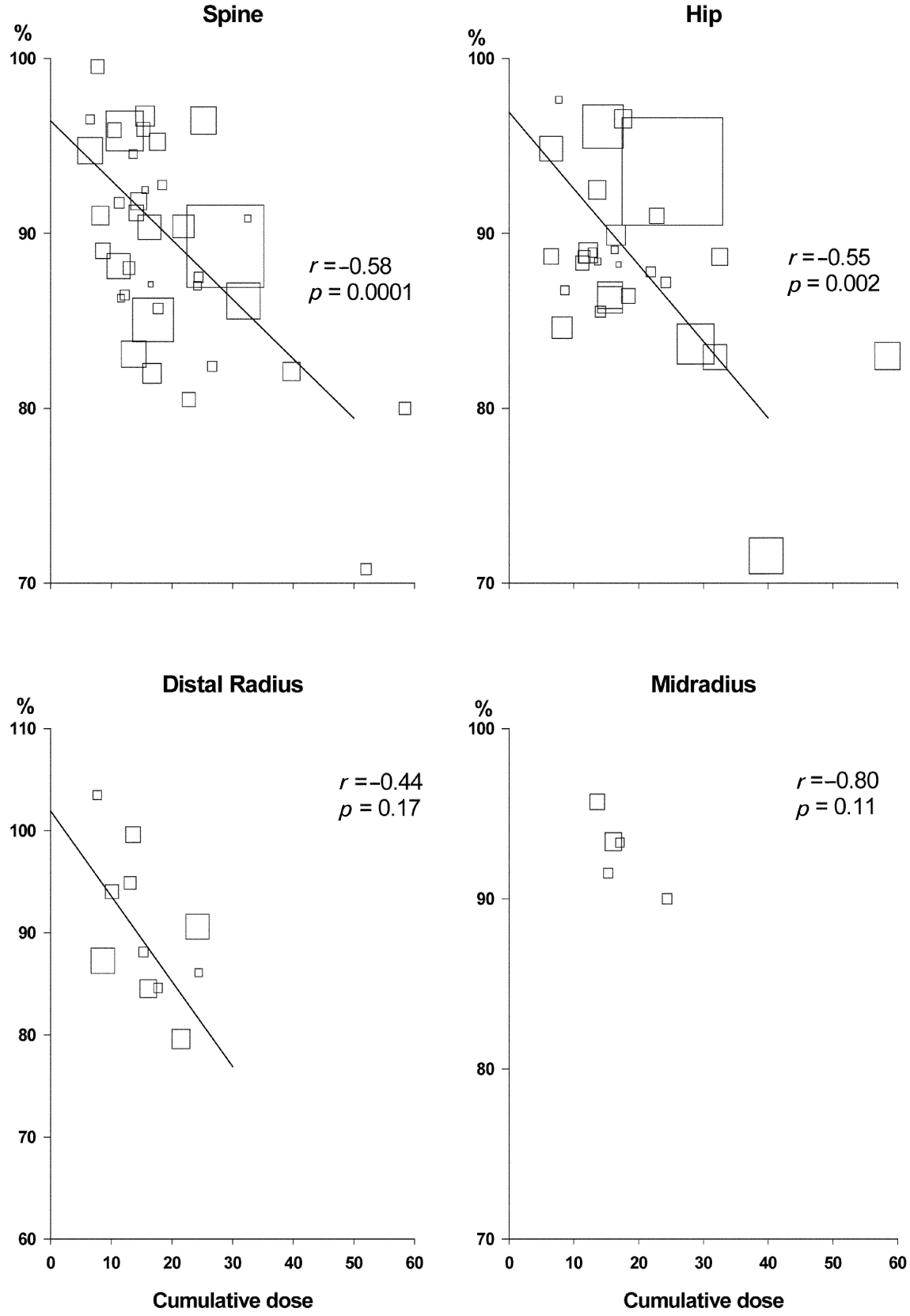

Fig. 2. Percentage of normal for spine, hip, distal and mid radius BMD stratified by cumulative CS dose across different studies, with size of estimates proportional to the number of CS users.

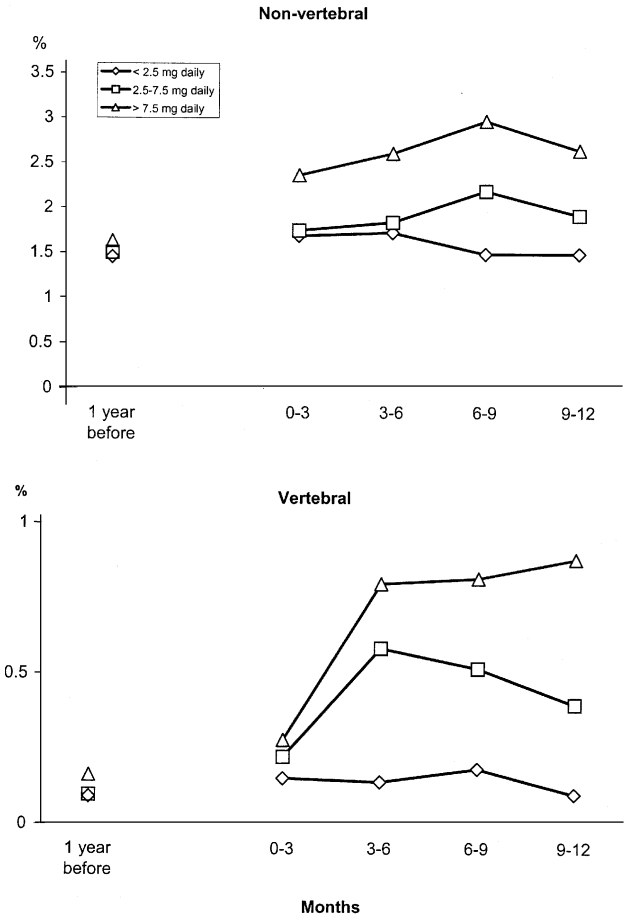

Fig. 3. Risk of non-vertebral and vertebral fracture before and during first year of CS therapy stratified by dose.

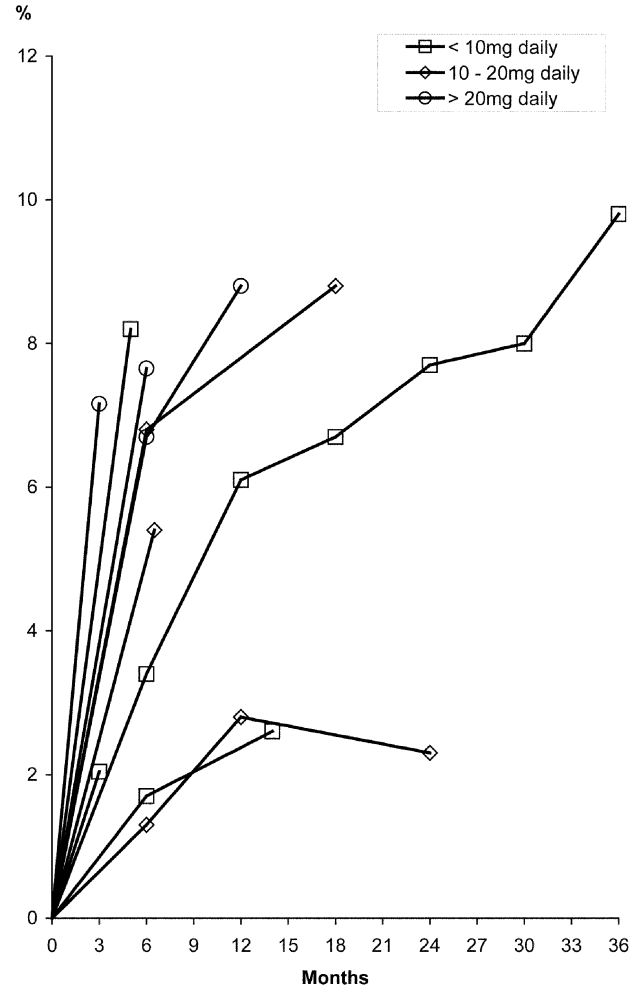

Fig. 4. Loss of spine BMD after start of CS therapy in ten longituinal studies.

patients with continued high dose CS therapy, the rate of fracture did not change substantively [75]. The risk of vertebral fractures also increased greatly in the high dose group.

The GPRD study findings are consistent with the high rate of new vertebral fractures within the first year of CS therapy found in four randomized clinical trials, with the rate in the calcium-treated placebo group ranging from 8 to 17% [106–109]. However, the finding of rapid onset of fracture was not observed in two smaller studies [110,111]. Interestingly, two studies conducted in parallel under similar protocol found no differences in the risk of vertebral fractures between new and long-term CS users. In patients who had been treated for 3 months or less prior to enrollment, the rate of new vertebral fracture in the first year of therapy was 17.3% in the placebo group [108], compared to 15.0% in placebo patients who previously had been treated for an average of 5.2 years [112]. However, spine BMD decreased by 2.8% in the first-time CS users and hip BMD by 3.1%, whereas there were no changes in long-term users [108,112].

The onset of bone loss is rapid within the first months of starting CS therapy, slowing down after about one year of therapy. Figure 4 shows the bone loss from the spine of first-time user followed in longitudinal studies [9,20,25,33,38,42,51,56,67,71]. One limitation of evaluating bone loss longitudinally is that daily dose may vary and reduce over time. A histomorphometric study of 16 patients starting CS therapy (10–25 mg/day) found that there was severe trabecular bone loss in the first 6 months of therapy, with much slower bone loss thereafter [113].

Offset of Skeletal Effects

Whether the increased risks of bone loss and fracture with CS use persist following discontinuation of therapy is an important consideration. There is strong evidence that suggests that corticosteroid-induced osteoporosis and its consequences are substantially reversible after CS therapy is stopped. In the GPRD study, most of the excess risk of fracture disappeared within 1 year of stopping therapy. This effect was most pronounced for vertebral fractures, but was also apparent for hip

fractures [75]. It was also noted that the rates of fracture also decreased in patients with a higher level of previous exposure when they stopped CS therapy [76]. A small cross-sectional study reported comparable rates of vertebral fracture in past CS users and controls [41].

Furthermore, two cross-sectional studies found that the BMD of past CS users was comparable to that of non-users [28,41] and a longitudinal study found substantial increases in BMD after discontinuation of CS therapy [38]. In addition, studies in patients who were cured of Cushing's syndrome reported normal BMD. A study of 17 patients found that whereas patients with active Cushing's syndrome have a substantially reduced BMD, previously cured patients had normal BMD [114]. A morphometric analysis in two cured Cushing's patients found a dramatic renewal of osteoblastic activity, with extended osteoid surfaces and normal appositional rate [115].

Susceptibility to Skeletal Effects

Not all patients using CS therapy develop a fracture. It is thus of interest to establish whether there are patient characteristics, such as age, sex, or underlying disease that predispose patients to fracture. The GPRD study found that the RR of fracture with CS therapy was similar across age, sex, or underlying disease. For example, the risk of hip fractures was increased by 59% in female users and by 67% in male users. Also, patients with obstructive pulmonary disease showed comparable increases in risk of fracture compared to patients with arthropathies [77]. Other studies have published conflicting results on individual susceptibility to fractures. Naganathan et al. [52] observed a higher increase in vertebral deformities in older users compared to younger users, whereas Peel et al. [57] observed the converse.

The results of various BMD studies are clearly inconsistent. Ruegsegger et al. [104] reported that younger people are more susceptible than the elderly, but other studies reported an absence of age effect [35,61,66,101]. Similarly, conflicting results were reported for sex: some studies have shown women to be more susceptible [12,37,48]; another study has observed increased effects in men [49]; whereas others found no major differences between men and women [11,21,61,64,101]. With respect to underlying disease, two studies have reported no differences in the effects of CS in patients with rheumatic or lung disease [14,61]. Overall, the effects of cumulative CS dose on BMD were not influenced by age or sex in this review.

Relationship Between BMD, Architecture and Risk of Fracture

Significant interest in establishing the relative roles of density and micro-architectural bone changes in corticosteroid-induced osteoporosis was triggered by Luengo et al.'s [116] findings of an association between BMD and vertebral fracture. They observed that the rate of vertebral fracture was substantially higher in CS users than in patients with idiopathic osteoporosis, attributed to direct deleterious effects of CS therapy on bone architecture [116]. Selby et al. [117], however, had contrasting results: vertebral fractures occurred at similar levels of BMD in CS users and non-users. But they also found that CS users had statistically significantly more vertebral fractures than non-users despite the similarity in BMD [117]. Thus, the data by Selby et al. do not provide compelling evidence that CS-induced bone fragility is caused primarily by BMD rather than micro-architectural changes.

The possible importance of changes in bone quality affected by CS therapy can be evaluated by assessing whether increases in fracture risk correspond closely to observed BMD changes. Peel et al. [57] found that there was a six-fold increase in the risk of vertebral deformity in CS users compared with controls, but only a 0.79 SD reduction in lumbar spine BMD. Table 2 shows the relationship between BMD changes and increases in risk of fracture. Based on the results of the regression analysis, it was estimated that a cumulative dose of 13.9 g would correspond to an expected BMD loss versus

Table 2. Relationship between BMD changes and risk of fracture

Site	Cumulative dose	Estimated BMD change as % normal (*Z*-score)[a]	Expected RR of fracture[b]	Observed RR of fracture at site (GPRD)[c]	Observed RR of fracture at site (other studies)[d]
Spine	1.5 g	–0.5% (–0.05)	1.04	2.40	–
	13.9 g	–4.7% (–0.5)	1.48	3.05	2.86
Hip	1.5 g	–0.7% (–0.04)	1.04	1.54	–
	13.9 g	–6.1% (–0.4)	1.41	2.34	2.01

[a]*Z*-score of –1 was taken to correspond to a 10% BMD reduction below normal at the spine and 17% of the hip.
[b]Based on estimates from Marshall et al: RR of vertebral fracture is 2.3 for –1 *Z*-score change in BMD, for hip fracture this is 2.6 [118]
[c]Based on GRPD estimates in patients using cumulative doses of 0.5–5 g and >10 g, respectively.
[d]Based on estimates from fracture studies other than GPRD that had an across-study average cumulative dose of 13.9 g.

normal of 4.7% at the spine and 6.1% at the hip. Using data from a meta-analysis on the relationship between BMD changes and fracture [118], this BMD change correlates to an expected RR of 1.48 for vertebral fracture and 1.41 for hip fracture [118]. The observed RRs of vertebral fractures were 3.05 in the GPRD study and 2.86 in the non-GPRD fracture studies. For hip fractures, the observed RRs were also comparable (2.34 and 2.01, respectively). Thus, these data suggest that fractures occur at much higher rates than expected on the basis of BMD changes. BMD changes during CS therapy may only predict to a moderate extent the increases in fracture risk.

Comparison of fracture rates in the placebo groups of several clinical trials found that there was a much higher incidence of vertebral fractures in patients with corticosteroid-induced osteoporosis compared to those with postmenopausal osteoporosis, despite a higher baseline BMD in patients with corticosteroid-induced osteoporosis. This strongly suggests that the risk of fracture may indeed be substantially higher in corticosteroid-induced osteoporosis at a similar level of BMD compared to postmenopausal osteoporosis [119]. Histomorphometric reports indicate that bone loss due to CS therapy occurs predominantly by trabecular thinning rather than by perforations or disconnections of trabecula as in idiopathic osteoporosis [120,121]. This suggests that the trabecular micro-architecture may be not be disrupted with CS therapy, except in the most severe cases of trabecular thinning.

Confounding by Underlying Disease

Patients using CS often have complicated systemic disorders that may lead to bone loss, independently of CS therapy. In studies with two control groups (one with the same disease as the CS users and one without disease), it was found that lumbar spine BMD of the CS users was on average 10.1% lower than that expected for a group of similar age and sex (23 studies; 777 CS users). For the disease control group, the figure was 3.6%. For hip BMD, these figures were 11.2% and 6.2%, respectively (16; 597). This information suggests that a substantial part of BMD loss is related to CS therapy.

Discussion

The results of our meta-analysis led to the suggestion that CS therapy is associated with a dose-related increase in risk of fracture and BMD loss. These effects may be substantially reversible after stopping therapy and are independent of underlying disease, age and sex. Inhaled CS therapy has been associated with increased loss of BMD [122]. However, a large cohort study found that users of inhaled CS therapy had higher risks of fracture, but that this excess risk was related to the underlying respiratory disease rather than to inhaled CS therapy [123].

Limitations of Review

The results of several studies were conflicting which may be due to a number of reasons: (i) large statistical variability due to small number of patients and measurements; (ii) imprecise estimates of CS dose schedules, incomplete information on the patients' compliance and varying definitions of CS exposure; (iii) imprecision and less sensitive and varying locations of the BMD measurements; and (iv) selection of an inappropriate control group. In addition, there are also limitations specific to this review. Summary information from individual studies that had varying methods of data collection such as BMD measurements was used. Comparisons between CS users and non-users that were made within each study could confound results if the magnitude of BMD reductions varied substantively between techniques. However, this limitation of the analysis to studies that used DXA and adjustment for BMD technique did not alter the results. The analysis was also limited to published information: effects of negative unpublished studies cannot be assessed.

Daily Dose versus Cumulative Dose

One of the unexpected findings in the large GPRD study was the early increase in risk of fracture in CS users, which was strongly related to the daily dose [75,76]. The effects of cumulative dose on risk of fracture were much less pronounced than those of daily dose [76]. In contrast, this review found a strong relationship between cumulative dose and BMD, and a much weaker relationship to daily dose. The BMD results would suggest increases in risk of fracture, which would start slowly after beginning of therapy but increase proportionally with duration of use. So, how can we explain those apparently contrasting results?

Bias may be one explanation; although it is too difficult to exclude all potential biases, it was considered unlikely in the GPRD study that bias is the explanation for the early daily dose-related increases in risk of fracture [75]. Also, the assessment of the independent effects of daily and cumulative dose is complicated by their close correlation. Nevertheless, it should be noted that the GPRD and BMD studies included different populations with varying patterns of CS use. The GPRD study was based on patients from a general practice setting, who mostly used CS intermittently with relatively few chronic users and patients with rheumatoid arthritis [79]. In contrast, the BMD studies were primarily conducted in specialist centers, in predominantly patients with rheumatoid arthritis using CS continuously over prolonged periods of time. This suggests that there may be two main mechanisms underlying the increased risk of fracture.

A key mechanism of corticosteroid-induced bone loss is a decrease in the rate of bone formation. Corticoster-

oid excess has been found to promote the apoptosis of osteoblasts [124]. The result is a relative increase in bone resorption at the basic multicellular units, the sites of bone remodeling. As only a small part of bone is being remodeled at one point in time, changes in BMD will only occur slowly. Chronic CS exposure is likely to cause the largest BMD reductions with repeated effects on newly active remodeling units. In contrast, daily dose is less likely to be a major determinant, given the delayed onset and the relatively small number of remodeling sites. Studies of bone markers have provided further evidence of the inhibition of bone formation. A dose-related reduction in osteocalcin levels has been found within the first 24 hours of CS therapy [125], which is rapidly reversible [126]. The second mechanism could be osteocyte apoptosis, as proposed by Manolagas [127]. Osteocytes are the most abundant cell type in bone and originate from osteoblasts. Although their precise function is unknown, apoptosis could lead to a deterioration of bone quality and early increases in fracture risk [127]. Osteocyte apoptosis was found to be prevalent in corticosteroid-induced osteoporosis [124]. Also, bisphosphonates have a protective effect against fracture despite relatively small increases in BMD and they have been shown to prevent osteocyte and osteoblast apoptosis [128]. Interestingly, daily dose is a strong determinant for avascular necrosis of bone, which can lead to a collapse of the femoral head and which can occur shortly after start of CS therapy [129]. Osteocyte apoptosis was found to be prevalent in patients with this disease [130]. Thus, bone fracture could possibly be the result of a less severe apoptosis than avascular necrosis of bone. If this hypothesis is correct, a strong correlation between fracture risk and daily dose, as observed in the GPRD study [75,76], could indeed be expected given the large number of osteocytes.

Management of Corticosteroid-Induced Osteoporosis

Various guidelines have been developed for the therapy and prevention of corticosteroid-induced osteoporosis [4,5]. The results of our review suggest that the risk of fracture appears shortly after start of therapy and at relatively low daily doses, with an increase in risk observed with use of doses above 5 mg/day. The risk appears to be substantially reversible after discontinuation of therapy. We therefore propose that preventive measures against corticosteroid-induced osteoporosis should be given parallel to the CS therapy in patients using daily doses above 5 mg, especially in patients with a high risk of fracture. High-risk patients may include patients aged 65 years or older, or those with a low baseline BMD or fracture history. It is also likely that the BMD threshold for fracture is different in corticosteroid-induced osteoporosis compared to postmenopausal osteoporosis.

References

1. Cushing H. The basophilic adenomas of the pituitary body and their clinical manifestations (pituirary basophilism). Bull Johns Hopkins Hosp 1932;1:137–92.
2. Guyatt GH, Webber CE, Mewa AA, Sackett DL. Determining causation–a case study: adrenocorticosteroids and osteoporosis. J Chron Dis 1984;37:343–52.
3. Haynes RC, Murad F. Adrenocortical steroids and their synthetic analogues. In: Gillman AG, Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. New York: MacMillan, 1980:1486–7.
4. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum 2001;44:1496–503.
5. Eastell R, Reid DM, Compston J, et al. A UK consensus group on management of glucocorticoid induced osteoporosis: an update. J Intern Med 1998;244:271–92.
6. Berntsen GKR, Fonnebo V, Tollan A, Sogaard AJ, Magnus JH. Forearm bone mineral density by age in 7,620 men and women: the Tromso study, a population-based study. Am J Epidemiol 2001;153:465–73.
7. Looker AC, Wahner HW, Dunn WL, et al. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int 1998;8:468–89.
8. Wahner HW, Fogelman I. The evaluation of osteoporosis: dual energy X-ray absorptiometry in clinical practice. London: Martin Dunitz, 1999:230–1.
9. Adachi JD, Benson WG, Bell MJ, et al. Corticosteroid-induced osteoporosis: follow-up over 3 years. In: Christiansen C, Overgaard K, ed. Osteoporosis 1990 (3), Third International Symposium on Osteoporosis. Copenhagen: Osteoporosis APS, 1990:1745–7.
10. Adinoff AD, Hollister JR. Steroid-induced fractures and bone loss in patients with asthma. N Engl J Med 1983;309:265–8.
11. Als OS, Gotfredsen A, Christiansen C. The effects of glucocorticoids on bone mass in rheumatoid arthritis patients. Arthritis Rheum 1985;28:369–75.
12. Bernstein CN, Seeger LL, Sayre W, Anton PA, Artinian L, Shanahan F. Decreased bone density in inflammatory bowel disease is related to corticosteroid use and not disease diagnosis. J Bone Miner Res 1995;10:250–6.
13. Bikle DD, Halloran B, Fong L, Steinbach L, Shellito J. Elevated 1,25-dihydroxyvitamin D levels in patients with chronic obstructive pulmonary disease treated with prednisone. J Clin Endocrinol Metab 1993;76:456–61.
14. Brandli DW, Golde G, Greenwald M, Silverman SL. Glucocorticoid-induced osteoporosis: a cross-sectional study. Steroids 1991;56:518–23.
15. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Effects of low dose corticosteroids on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol 1995;22:1055–9.
16. Butler RC, Davie MWJ, Worsfold M, Sharp A. Bone mineral content in patients with rheumatoid arthritis: relationship to low-dose steroid therapy. Br J Rheumatol 1991;30:86–90.
17. Cortet B, Flipo RM, Blanckaert F, Duquesnoy B, Marchandise X, Delcambre B. Evaluation of bone mineral density in patients with rheumatoid arthritis. Rev Rhum Engl Ed 1997;64:451–8.
18. Deuxchaisnes de NC, Devogelaer JP, Esselinckx W, et al. The effect of low dosage glucocorticoids on bone mass in rheumatoid arthritis: a cross-sectional and a longitudinal study using single photon absorptiometry. Exp Med Biol 1984;171:209–39.
19. Dhillon VB, Davies MC, Hall ML, et al. Assessment of the effect of oral corticosteroids of bone mineral density in systemic lupus erythematosus: a preliminary study with dual energy X ray absorptiometry. Ann Rheum Dis 1990;49:624–6.
20. Dolan AL, Moniz C, Dasgupta B, et al. Effects of inflammation and treatment on bone turnover and bone mass in polymyalgia rheumatica. Arthritis Rheum 1997;11:2022–9.

21. Ebeling PR, Erbas B, Hopper JL, Wark JD, Rubinfeld AR. Bone mineral density and bone turnover in asthmatics treated with long-term inhaled or oral glucocorticoids. J Bone Miner Res 1998;13:1283–9.
22. Evans SF, Davie MJW. Vertebral fractures and bone mineral density in idiopathic, secondary and corticosteroid associated osteoporosis in men. Ann Rheum 2000;59:269–75.
23. Formiga F, Moga I, Nolla JM, Pac M, Mitjavila F, Roig-Escofet D. Loss of bone mineral density in premenopausal women with systemic lupus erythematosus. Annals of Rheumatic Diseases 1995;54:274–6.
24. Formiga F, Nolla JM, Mitjavila F, Navarro MA, Moga I. Bone mineral density and hormonal status in man with systemic lupus erythematosus. Lupus 1996;5:623–6.
25. Fujita T, Satomura A, Hidaka M, Ohsawa I, Endo M, Ohi H. Acute alteration in bone mineral density and biochemical markers for bone metabolism in nephritic patients receiving high-dose glucocorticoid and one-cycle etidronate therapy. Calcif Tissue Int 2000;66:195–9.
26. Garton MJ, Reid DM. Bone mineral density of the hip and of the anteroposterior and lateral dimentions of the spine in men with rheumatoid arthritis. Arthritis Rheum 1993;36:222–8.
27. Gluck OS, Murphy WA, Hahn TJ, Hahn B. Bone loss in adults receiving alternative day glucocorticoid therapy. Arthritis Rheum 1981;24:892–8.
28. Hall GM, Spector TD, Griffin AJ, Jawad ASM, Hall ML, Doyle DV. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. Arthritis Rheum 1993;36:1510–6.
29. Hansen M, Florescu A, Stoltenberg M, et al. Bone loss in rheumatoid arthritis. Scand J Rheumatol 1996;25:367–76.
30. Haugeberg G, Myklebust G, Dovland H, Mikkelsen B, Gran JT. No permanent reduction in bone mineral density during treatment of polymyalgia rheumatica and temporal arteritis using low dose corticosteroids. Scand J Rheumatol 2000;29:163–9.
31. Houssiau FA, Lefebvre C, Depresseux G, Lambert M, Devogelaer JP, Nagant de Deuxchaisnes C. Trabecular and cortical bone loss in systemic lupus erythematosus. Br J Rheumatol 1996;35:244–7.
32. Javaid MK, McCrudden PR, Taylor P, et al. Comparison of calcaneal ultrasound and DXA to assess the risk of corticosteroid-induced osteoporosis: a cross-sectional study. Osteoporos Int 2001;12:788–93.
33. Julian AB, Laskow DA, Dubovsky J, Dubovsky EV, Curtis JJ, Quarles LD. Rapid loss of vertebral moneral density after renal transplantation. N Engl J Med 1991;325:544–50.
34. Kalla AA, Fataar AB, Jessop SJ, Bewerunge L. Loss of trabecular bone mineral density in systemic lupus erythematosus. Arthritis Rheum 1993;36:1726–34.
35. Kipen Y, Buchbinder R, Forbes A, Strauss B, Littlejohn G, Morand E. Prevalence of reduced bone mineral density in systemic lupus erythematosus and the role of steroids. J Rheumatol 1997;24:1922–9.
36. Kröger H, Honkanen R, Saarikoski S, Alhava E. Decreased axial bone mineral density in perimenopausal women with rheumatoid arthritis–a population based study. Ann Rheum Dis 1994;53:18–23.
37. Laan RFJM, van Riel PLCM, van Erning LJTO, Lemmens JAM, Ruijs SHJ, van de Putte LBA. Vertebral osteoporosis in rheumatoid arthritis patients: Effects of low dose prednisone therapy. Br J Rheumatol 1992;31:91–6.
38. Laan RFJM, van Riel PLCM, van de Putte LBA, van Erning LJTO, van't Hof MA, Lemmens JAM. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. Ann Intern Med 1993;119:963–8.
39. Laan RFJM, Buijs WCAM, van Erning LJTO, et al. Differential effects of glucocorticoids on cortical appendicular and cortical vertebral bone mineral content. Calcif Tissue Int 1993;52:5–9.
40. Laatikainen AK, Kröger HPJ, Tukiainen HO, Honkanen RJ, Saarikoski SV. Bone mineral density in perimenopausal women with asthma. Am J Respir Crit Care Med 1999;159:1179–85.
41. Lane NE, Pressman AR, Star VL, Cummings SR, Nevitt MC. Rheumatoid arthritis and bone mineral density in elderly women. J Bone Miner Res 1995;10:257–63.
42. Lange U, Boss B, Teichmann J, Stracke H, Neeck G. Bone mineral density and biochemical makers of bone metabolism in late onset rheumatoid arthritis and polymyalgia rheumatoid – a prospective study on the influence of glucocorticoid therapy. Z Rheumatol 2000;59 Suppl 2:137–41.
43. Leboff MS, Wade JP, Mackowiak S, Fuleihan GE, Zangari M, Liang MH. Low dose prednisone does not affect calcium homeostasis or bone density in postmenopausal women with rheumatoid arthritis. J Rheumatol 1991;18:339–44.
44. Lespessailles E, Poupon S, Adriambelosoa N, et al. Glucosteroid-induced osteoporosis: is bone density decrease the only explanation? Joint Bone Spine 2000;67:119–26.
45. Lespessailles E, Siroux V, Poupon S, et al. Long-term corticosteroid therapy induces mild changes in trabecular bone texture. J Bone Miner Res 2000;15:747–53.
46. Li EK, Tam LS, Young RP, Ko GTC, Li M, Lau EMC. Loss of bone mineral density in Chinese pre-menopausal women with systemic lupus erythematosus treated with corticosteroids. Br J Rheumatol 1998;37:405–10.
47. Martin JC, Munro R, Campbell MK, Reid DM. Effects of disease and corticosteroids on appendicular bone mass in postmenopausal woman with rheumatoid arthritis: comparison with axial measurements. Br J Rheumatol 1997;36:43–9.
48. Marystone JF, Barrett-Connor EL, Morton DJ. Inhaled and oral corticosteroids: their effects on bone mineral density in older adults. Am J Public Health 1995;85:1693–5.
49. Mateo L, Nolla JM, Rozadilla A, et al. Bone mineral density in patients with temporal arthritis and polymyalgia rheumatica. J Rheumatol 1993;20:1369–73.
50. Mateo L, Nolla JM, Bonnin MR, Navarro MA, Roig-Escofet D. Sex hormone status and bone mineral density in men with rheumatoid arthritis. J Rheumatol 1995;22:1455–60.
51. McKenzie R, Reynolds JC, O'Fallon A, et al. Decreased bone mineral density during low dose glucocorticoid administration in a randomised-placebo controlled trial. J Rheumatol 2000;27:2222–5.
52. Naganathan V, Jones G, Nash P, Nicholson G, Eisman J, Sambrook PN. Vertebral fracture risk with long-term corticosteroid therapy. Arch Intern Med 2000;160:2917–22.
53. Napal J, Cuerno Y, Olmos JM, Riancho JA, Amado JA, González Macías J. Modificaciones de la masa ósea en la cirrosis hepatica, la enfermedad pulmonary obstructiva crónica, la diabetes dependiente de la insulina y el hiperparatiroidismo primario. Med Clin (Barc) 1993;100:576–9.
54. Nolla JM, Fiter J, Gomez Vaquero C, Mateo L, Valverde J, Roig Escofet D. Estudio densitométrico en mujeres posmenopáusicas con arthritis reumatoide tratadas con dosis bajas de glucocorticoides. Med Clin Barc 2000;114:452–3.
55. Packe GE, Douglas JG, McDonald AF, Robins SP, Reid DM. Bone density in asthmatic patients taking high dose inhaled beclomethasone dipropionate and intermittent systemic corticosteroids. Thorax 1992;47:4147.
56. Pearce G, Ryan PFJ, Delmas PD, Tabensky DA, Seeman E. The deleterious effects of low-dose corticosteroids on bone density in patients with polymyalgia rheumatica. Br J Rheumatol 1998;37:292–9.
57. Peel NFA, Moore DJ, Barrington NA, Bax DE, Eastell R. Risk of vertebral fracture and relationship to bone mineral density in steroid treatment rheumatoid arthritis. Ann Rheum Dis 1995;54:801–6.
58. Peretz A, Praet JP, Rozenberg S, Bosson D, Famaey JP, Bourdoux P. Osteocalcin and bone mineral content in rheumatoid arthritis. Clin Rheumatol 1989;8:42–8.
59. Pons F, Peris P, Guañabens N, Font J, Huguet M, Espinosa G, Ingelmo M, Muñoz-Gomez J, Setoain J. The effects of systemic lupus erythematosus and long-term steroid therapy on bone mass in pre-menopausal women. Br J Rheumatol 1995;34:742–6.
60. Praet JP, Peretz A, Rozenberg S, Famaey JP, Bourdoux P. Risk of osteporosis in men with chronic bronchitis. Osteoporos Int 1992;2:257–61.

61. Reid IR, Heap SW. Determinants of vertebral mineral density in patients receiving long term glucocorticoid therapy. Arch Intern Med 1990;150:2545–8.
62. Reid IR, Evans MC, Wattie DJ, Ames R, Cundy TF. Bone mineral density of the proximal femur and lumbar spine in glucocrticoid-treated asthmatic patients. Osteoporos Int 1992; 2:103–5.
63. Reid IR, Evans MC, Stapleton J. Lateral spine densitometry is a more sensitive indicator of glucocorticoid-induced bone loss. J Bone Miner Res 1992;7:1221–5.
64. Rizzato G, Tosi G, Mella C, Montemurro L, Zanni D, Sisti S. Prednisone-induced bone loss in sarcoidosis: a risk especially frequent in postmenopausal women. Sarcoidosis 1998:5:93–8.
65. Sambrook PN, Eisman JA, Yeates MG, Pocock NA, Eberl S, Champion GD. Osteoporosis in rheumatoid arthritis: safety of low dose corticosteroids. Ann Rheum Dis 1986;45:950–3.
66. Sambrook PN, Birmingham J, Kempler S, et al. Corticosteroids effects on proximal femur bone loss. J Bone Miner Res 1990;5:1211–6.
67. Sambrook PN, Kelly PJ, Fontana D, et al. Mechanisms of rapid bone loss following cardiac transplantation. Osteoporos Int 1994;4:273–6.
68. Sambrook PN, Raj A, Hunter D, Naganathan V, Mason R, Robinson B. Osteoporosis with low dose corticosteroids: contribution of underlying disease effects and discriminatory ability of ultrasound versus bone densitometry. J Rheumatol 2001;28:1063–7.
69. Schaadt O, Bohr H. Bone mineral in lumbar spine, femoral neck and femoral shaft measured by dual photon absorptiometry with 153-gadolineum in prednisone treatment. Adv Exp Med Biol 1984;171:201–8.
70. Shane E, Rivas MDC, Silverberg SJ, Kim TS, Staron Rb, Bilezikian JP. Osteoporosis after cardiac transplantation. Am J Med 1993;94:257–64.
71. Shane E, Rivas M, Staron RB, et al. Fracture after cardiac transplantation: a prospective longitudinal study. J Clin Endocrinol Metab 1996;81:1740–6.
72. Stellon AJ, Davies A, Compston J, Williams R. Bone loss autoimmune chronic active hepatitis on maintenance corticosteroid therapy. Gastroenterology 1985;89:1078–83.
73. van Berkum FNR, Beukers R, Birkenhager JC, Kooij PPM, Schalm SW, Pols HAP. Bone mass in women with primary biliary cirrhosis. The relation with histological stage and use of glucocorticoids. Gastroenterology 1990;99:1134–9.
74. Verstraeten A, Dequeker J. Vertebral and peripheral bone mineral content and fracture incidence in postmenopausal patients with rheumatoid arthritis; effects of low dose corticosteoids. Ann Rheum Dis 1986;45:852–7.
75. van Staa TP, Leufkens HGM, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000;15:993–1000.
76. van Staa TP, Leufkens HGM, Abenhaim L, Zhang B, Cooper C. Fractures and oral corticosteroids: relationship to daily and cumulative dose. Rheumatol 2000;39:1383–9.
77. van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HGM. The use of a large pharmacoepidemiological database to study exposure to oral corticosteroids and risk of fractures: validation of study population and results. Pharmacoepi Drug Saf 2000;9:359–66.
78. van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HGM. Public health impact of adverse bone effects of oral corticosteroids. Br J Clin Pharmacol 2001;51:601–7.
79. van Staa TP, Cooper C, Abenhaim L, Begaud B, Zhang B, Leufkens HGM. Utilisation of oral corticosteroids in the United Kingdom. Q J Med 2000;93:105–11.
80. Anderson R, Rundgren A, Rosengren K, Bengtsson BA, Malmvall BE, Mellstrom D. Osteoporosis after long-term corticosteroid treatment of giant cell arteritis. J Intern Med 1990;227:391–5.
81. Ballzan MA, Suissa S, Bauer DC, Cummings SR. Hip fractures attributed to corticosteroid use. Lancet 1999;353:1327.
82. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. Ann Rheum Dis 1995;54:49–52.
83. Fitzsimons R, Grammer LC, Halwig JM, Aksamit T, Patterson R. Prevalence of adverse effects in corticosteroid-dependent asthmatics. N Engl Reg Allergy Proc 1988;9:157–62.
84. Grisso JA, Kelsey JL, O'Brian LA, et al. and the hip fracture Study Group. Risk factors for hip fracture in men. Am J Epidemiol 1997;145:786–93.
85. Hooyman JR, Melton LJ, Nelson AM, O'Fallon M, Riggs BL. Fractures after rheumatoid arthritis. Arthritis Rheum 1984;27:1353–61.
86. Lems WF, Jahangier ZN, Jacobs JWG, Bijlsma JWJ. Vertebral fractures in patients with rheumatoid arthritis treated with corticosteroids. Clin Exp Rheumatol 1995;13:293–7.
87. McComkey B, Fraser GM, Bligh AS. Osteoporosis and purpura in rheumatoid disease: prevalence and relation to treatment with corticosteroids. J Med 1962;New Series XXXI, No 124:419–27.
88. McDougall R, Sibley J, Haga M, Russell A. Outcome in patients with rheumatoid arthritis receiving prednisone compared to matched controls. J Rheumatol 1994;21:1207–13.
89. McEvoy CE, Ensrud KE, Bender E, et al. Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:704–9.
90. Michel BA, Bloch DA, Fries JF. Predictors of fracture in early rheumatoid arthritis. J Rheumatol 1991;18:804–8.
91. Paganini-Hill A, Ross RK, Gerkins VR, Henderson BE, Arthur M, Mack TM. Menopausal estrogen therapy and hip fractures. Ann Intern Med 1981;95:28–31.
92. Rashiq S, Logan RFA. Role of drugs in fractures of the femoral neck. Br Med J 1986;292:861–3.
93. Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med 1994;96:115–23.
94. Saville PD, Kharmosh O. Osteoporosis of rheumatoid arthritis: influence of age, sex and corticosteroids. Arthritis Rheum 1967;10:423–30.
95. Tsugeno H, Goto B, Fujita T, et al. Oral glucocorticoid-induced fall in cortical bone volume and density in postmenopausal asthmatic patients. Osteoporos Int 2001;12:266–70.
96. Vestergaard P, Krogh K, Rejnmark L, Laurberg S, Mosekilde L. Fracture risk is increased in Crohn's disease, but not in ulcerative colitis. Gut 2000;46:176–81.
97. Walsh LJ, Wong CA, Oborne J, et al. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. Thorax 2001;56:279–84.
98. Miyamoto S, Kageyama Y, Ozeki T, Hiyoshi M, Suzuki M, Inoue T. Effects of glucocorticoids on bone mineral density in rheumatoid arthritis patients. Arch Orthop Trauma Surg 1999;119:18–21.
99. Tsugeno H, Nakai M, Okamoto M, et al. Bone mineral density in steroid-dependant asthma assessed by peripheral quantitive computed tomography. Eur Respir J 1999;14:923–7.
100. Ruegsegger P, Durand EP, Dambacher MA. Differential effects of aging and disease on trabecular and compact bone density of the radius. Bone 1991;12:99–105.
101. Dykman TR, Gluck OS, Murphy WA, Hahn TJ, Hahn BH. Evaluation of factors associated with glucocorticoid-induced osteopenia in patients with rheumatic diseases. Arthritis Rheum 1985;28:361–8.
102. Reid DM, Kennedy NSJ, Smith MA, Tothill P, Nuki G. Total body calcium in rheumatoid arthritis: effects of disease activity and corticosteroids treatment. Br Med J 1982;285:330–2.
103. Reid DM, Nicoll JJ, Smith MA, Higgins B, Tothill P, Nuki G. Corticosteroids and bone mass in asthma: comparisons with rheumatoid arthritis and polymyalgia rheumatica. Br Med J 1986;293:1463–6.
104. Ruegsegger P, Medici TC, Anliker. Corticosteroid-induced bone loss: a longitudinal study of alternative day therapy in patients with bronchial asthma using quantitative computed tomography. Eur J Clin Pharmacol 1983;25:615–20.
105. Jardinet D, Lefébvre C, Depresseux G, Lambert M, Devogelaer

JP, Houssiau FA. Longitudinal analysis of bone mineral density in pre-menopausal female systemic lupus erythematosus patients: deleterious role of glucocorticoid therapy at the lumbar spine. Rheumatology 2000;39:389–92.
106. Adachi J, Bensen WG, Brown J, et al. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. N Engl J Med 1997;337:382–7.
107. Boutsen Y, Jamart J, Esselinckx W, Stoffel M, Devogelaer JP. Primary prevention of glucocorticoid-induced osteoporosis with intermittent intravenous pamidronate: a randomised trial. Calcif Tissue Int 1997;61:266–71.
108. Cohen S, Levy RM, Keller M, et al. Risedronate therapy prevents corticosteroids-induced bone loss. Arthritis Rheum 1999;42:2309–18.
109. Healey JH, Paget SA, Williams-Russo P, et al. A randomised conrolled trial of salmon calcitonin to prevent bone loss in corticosteroid-treatment of temporal arteritis and polymyalgia rheumatica. Calcif Tissue 1996;58:73–80.
110. Boutsen Y, Jamart J, Esselinckx W, Devogelaer JP. Primary prevention of glucocorticoid-induced osteoporosis with intravenous pamidronate and calcium: a prospective controlled 1-year study comparing a single infusion, an infusion given once every 3 months, and calcium alone. J Bone Miner Res 2001;16:104–12.
111. Sambrook P, Birmingham J, Kelly P, et al. Prevention of corticosteroid osteoporosis. N Engl J Med 1993;328:1747–52.
112. Reid DM, Hughes RA, Laan RFJM, et al. Efficacy and safety of daily risedronate in the treatment of corticosteroids-induced osteoporosis in men and women; a randomised trial. J Bone Miner Res 2000;15:1006–13.
113. Lo Cascio VL, Bonucci E, Ballanti P, et al. Glucocorticoid osteoporosis: a longitudinal study. In: Christiansen C. Osteoporosis APS Copenhagen, Osteoporosis 1987;1044–6.
114. Manning PJ, Evans MC, Reid IR. Normal bone mineral density following cure of Cushing's syndrome. Clin Endocrinol 1992;36:229–34.
115. Bressot C, Meunier PJ, Chapuy MC, Lejeune E, Edouard C, Darby AJ. Histomorphometric profile, pathophysiology and reversibility of corticosteroid-induced osteoporosis. Metab Bone Dis Rel Res 1979;1:303–11.
116. Luengo M, Picado C, Del Rio L, Guanabens N, Montserrat JM, Setoain J. Vertebral fractures in steroid dependant asthma and involutional osteoporosis: a comparative study. Thorax 1991;46:803–6.
117. Selby PL, Halsey JP, Adams KRH, et al. Corticosteroids do not alter the threshold for vertebral fracture. J Bone Miner Res 2000;15:952–6.
118. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. Br Med J 1996;312:1254–9.
119. Clowes JA, Peel N, Eastell R. Glucocorticoid-induced osteoporosis. Curr Opin Rheumatol 2001;13:326–32.
120. Aaron JE, Francis RM, Peacock M, Makins NB. Contrasting microanatomy of idiopathic and corticosteroid-induced osteoporosis. Clin Orthop 1989;243:294–305.
121. Chappard D, Legrand E, Basle MF, et al. Altered trabecular architecture induced by corticosteroids: a bone histomorphometric study. J Bone Miner Res 1996;11:676–85.
122. Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, LaHive K, LeBoff MS. Effects of inhaled glucocorticoids on bone density in premenopausal women. N Engl J Med 2001;345:941–7.
123. van Staa TP, Leufkens HGM, Cooper C. Use of inhaled corticosteroids and risk of fractures. J Bone Miner Res 2001;3:581–8.
124. Weinstein RS, Jilka RL, Parfitt M, Manolagas SC. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids: potential mechanisms of their deleterious effects on bone. J Clin Invest 1998;102:274–82.
125. Reid IR, Chapman GE, Fraser TRC. Low serum osteocalcin levels in glucocorticoid-treated asthmatics. J Clin Endocrin Metab 1986;62:379–83.
126. Godshalk MF, Downs RW. Effect of short-term glucocorticoids on serum osteocalcin in healthy young men. J Bone Miner Res 1988;3:113–5.
127. Manolagas SC. Corticosteroids and fractures: a close encounter of the third cell kind (editorial). J Bone Miner Res 2000;15:1001–5.
128. Plotkin LI, Weinstein RS, Parfitt AM, Roberson PK, Manolagas SC, Bellido T. Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin. J Clin Invest 1999;104:1363–74.
129. Felson DT, Anderson JJ. Across-study evaluation of association between steroid dose and bolus steroids and vascular necrosis of bone. Lancet 1987;i:902–5.
130. Weinstein RS, Nicholas RW, Manologas SC. Apoptosis of osteocytes in glucocorticoid-induced osteonecrosis of the hip. J Clin Endocrinol Metab 2000;85:2907–12.

Received for publication 14 January 2001
Accepted in revised form 25 March 2002