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Oral corticosteroids and fracture risk: relationship to daily and cumulative doses

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Abstract

Objective. This study examined the effects of daily and cumulative oral corticosteroid doses on the risk of fractures.

Methods. Information was obtained from the General Practice Research Database, which contains medical records of general practitioners in England and Wales. The study included 244 235 oral corticosteroid users and 244 235 controls.

Results. Patients taking higher doses (at least 7.5 mg daily of prednisolone or equivalent) had significantly increased risks of non-vertebral fracture [relative rate (RR) = 1.44, 95% confidence interval (CI) 1.34–1.54], hip fracture (RR = 2.21, 95% CI 1.85–2.64) and vertebral fracture (RR = 2.83, 95% CI 2.35–2.40) relative to patients using oral corticosteroids at lower doses (less than 2.5 mg per day). Fracture risk was also elevated among people with higher cumulative exposure to oral corticosteroids over the study period, but this effect was almost wholly removed by adjustment for daily dose, age, gender and other confounding variables.

Conclusions. These findings suggest that the adverse skeletal effects of oral corticosteroids manifest rapidly and are related to daily dose. The level of previous exposure to oral corticosteroids was not a strong determinant of the risk of fracture. Preventive measures against corticosteroid-induced osteoporosis should therefore be instituted as soon after the commencement of glucocorticoid therapy as possible.

KEY WORDS: Osteoporosis, Epidemiology, Glucocorticoids, Fracture, Risk factors.

Osteoporosis is one of the most serious complications in patients receiving long-term oral corticosteroid treatment. It is well known that oral corticosteroid treatment leads to substantial and rapid loss of bone density. This bone loss is related to the dose and duration of oral corticosteroid therapy [1, 2]. However, there are few studies of the risk of fracture, the clinically important end-point of bone loss [3–18]. Most of these have been confined to patients with rheumatoid arthritis, have included only a small number of patients and have had correspondingly low statistical power. In one population-based study, the risk of hip fracture was doubled in patients taking oral corticosteroids compared with controls, but the differences did not remain statistically significant after adjustment for potential confounding variables [4]. There is limited information in these studies about the relationship of the risk of fracture with the oral corticosteroid dose. It is also not established whether increased risk of fracture is related to the daily dose or to the cumulative dose of corticosteroid, or to both of these. If this relationship were delineated better, strategies to prevent the adverse skeletal effects of oral corticosteroids could be targeted more effectively. This study was part of a larger study which aimed to evaluate the risk of fracture attributable to oral corticosteroid treatment [19]. In a previous report from this study, we presented the overall risks of vertebral and non-vertebral fracture among oral corticosteroid users compared with a control group who received non-systemic therapy (topical, aural, ophthalmic or nasal) [19]. The emphasis of that report was on the overall risk of fracture in relation to the duration of

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therapy, and the pattern of fracture risk after cessation of corticosteroid treatment. In the present paper we explore the effects of daily and cumulative corticosteroid doses on the risk of fracture. We wish to address specifically whether the risk of fracture associated with corticosteroid therapy is related to the daily dose or to the duration of use.

Subjects and methods

The data for this study were obtained from the General Practice Research Database (GPRD), which comprises the computerized medical records of general practitioners (GPs) in England and Wales. The study included 683 practices from different geographical areas of England and Wales. The data recorded in the GPRD include demographic information, prescription details, clinical events, the preventive care provided, specialist referrals, hospital admissions and their major outcomes [20–25]. Clinical data are stored and retrieved by means of OXMIS (Oxford Medical Information Systems) codes for diseases that are cross-referenced to the International Classification of Diseases, 9th revision (ICD-9) [21, 24]. Each entry in the GPRD is internally validated by cross-checking within the practice and by comparison with external statistics [20–25]. Only data from practices that pass this quality control are compiled to form the GPRD database. Several independent validation studies have confirmed that the GPRD has a high level of completeness and validity [26–29]. The GPRD is owned by the Department of Health in the UK.

Study population

Details of the methods used in the investigation and of the overall fracture results are available elsewhere [19]. In brief, a retrospective cohort study was conducted comparing patients using oral corticosteroids (aged 18 yr or older) with control patients. The oral corticosteroid users were patients who had received one or more prescriptions for oral corticosteroids during the period from the enrolment date of their practice in the GPRD until the end of the study (December 1997). Each oral corticosteroid user was matched to a control patient by age (within 5 yr or, if no patient was found, within 10 yr), gender and, if possible, medical practice. They were followed from the start of oral corticosteroid treatment until (i) they sustained a fracture; (ii) 91 days after the last oral corticosteroid prescription; or (iii) the patient's change of practice or death or the end of the study (whichever came first). The control patients were patients who received only non-systemic corticosteroid prescriptions (topical, aural, ophthalmic or nasal). The non-systemic corticosteroids included corticosteroid eye drops and ointments (British National Formulary 11.4.1), ear drops and ointments (12.1.1), nasal sprays (12.2.1), and topical skin creams, ointments and lotions (13.4) [30].

Cases were defined as patients who had a non-vertebral or vertebral fracture recorded in their medical records during follow-up. The classification of fractures was based on the ICD-9 categories. As part of the study, GPs were requested to confirm the diagnosis and to provide discharge summaries or diagnostic reports for 150 cases of hip fracture and 150 cases of vertebral fracture. Hip fracture was confirmed by the GP on the questionnaire in 91.0% of cases and by discharge summary in 85.2% of cases. Vertebral fracture was confirmed on the GP questionnaire in 88.1% of cases and verified against a radiographic report in 76.3% of cases. Of the 150 vertebral fractures, 96.4% were diagnosed radiographically, according to the GP questionnaire.

For each oral corticosteroid user, the daily dose over the total treatment period was estimated by dividing the total amount of prednisolone prescribed (or equivalent dose) in milligrams by the treatment time [30]. Three dose categories were assigned: low (less than 2.5 mg/day), medium (2.5–7.5 mg/day) and high (7.5 mg/day or more). The cumulative oral corticosteroid dose was estimated by reviewing at each oral corticosteroid prescription the total amount of prednisolone that had been prescribed at any time previously to the patient. Patients could move over time to higher cumulative dose categories if they received new oral corticosteroid prescriptions.

Statistical analysis

Incidence rates were estimated by dividing the number of patients with a fracture by the total number of person-years of follow-up. This method of estimating incidence is used widely when the duration of follow-up varies [31]. In our study population, there was significant variation in the duration of oral corticosteroid treatment. The mean number of oral prescriptions received was 6.8 and the median was 2. Cox proportional hazards models were used to calculate adjusted relative rates in the comparison between the different oral corticosteroid dose groups. Poisson regression was used in the analysis of the cumulative *vs* daily dose. Our method of analysis ensured that patients with longer follow-up contributed more information to the results.

As categorical analysis of continuous variables could inadvertently use cut-off points that are not biologically relevant, a non-parametric cubic spline regression model was used to estimate the relative rate of fracture over continuous daily dose [32–35]. No spline regression was conducted for doses greater than 20 mg/day because of the smaller number of patients taking these higher doses and the unstable regression models that would result. Data for the patients using these doses were combined and an adjusted relative rate was estimated, which was plotted at the midpoint of daily dose and connected by a straight line to the spline regression curve.

Results

Oral corticosteroids were prescribed to 244 235 patients. The cohort receiving oral corticosteroid was categorized into three groups according to the average daily dose over the treatment period. As shown in Table 1, there

were 50 649 subjects using low-dose oral corticosteroids (less than 2.5 mg/day prednisolone or equivalent), 104 833 people using a dose of 2.5–7.5 mg/day and 87 949 people using higher doses (7.5 mg or more daily). The median duration of steroid use was 28 days overall. This was highly skewed, 5% of subjects having follow-up durations longer than 5 yr. The duration of follow-up in the low-dose category was longer (median 2.5 yr) than in the medium- and high-dose categories (median 0.2 yr). There were 22 626 patients in the high-dose group with a follow-up of 6 months or more. Women accounted for around 61% of the low- and medium-dose groups and 54.5% of the high-dose group. The daily dose also increased with advancing age, such that the average ages were 55.5, 56.3 and 58.8 yr in the low-, medium- and high-dose groups, respectively. Non-vertebral fractures were reported in the year before baseline in 1.4% of the low-dose, 1.5% of the medium-dose and 1.6% of the high-dose corticosteroid users.

The incidence of non-vertebral fractures was 1.6 per 100 person-years in the lowest corticosteroid dose category compared with an incidence of 2.6 per 100 person-years in the highest dose category (Table 2). After adjustment for back pain, rheumatoid arthritis and a history of falling, the non-vertebral fracture incidence rate remained significantly higher in the high-dose category than in the low-dose users [relative rate 1.44; 95% confidence interval (95% CI) 1.34–1.54]. In the medium-dose category, the adjusted relative rate was 1.18 (95% CI 1.11–1.26). The risk of hip and vertebral fractures also increased with daily dose. The relative rate of hip fracture was 1.62 in the medium-dose group and 2.21 in the high-dose group compared with the low-dose group. The relative rates for vertebral fracture were 1.54 and 2.83, respectively.

Table 1. Characteristics of oral corticosteroid users stratified by daily dose

Characteristic	Dose		
	Low (n = 50 649)	Medium (n = 104 833)	High (n = 87 949)
Follow-up			
Total duration (person-years)	141 598	118 057	65 012
Mean duration (yr)	2.8	1.1	0.7
Median duration (yr)	2.5	0.2	0.2
Number of women	31 048 (61.3%)	63 650 (60.7%)	47 938 (54.5%)
Age (yr)			
Mean	55.5	56.3	58.8
Median	58	59	62
Medical condition			
Back pain year before	4383 (8.7%)	8705 (8.3%)	8476 (9.6%)
Rheumatoid arthritis	1153 (2.3%)	5388 (5.1%)	3416 (3.9%)
Falls year before	618 (1.2%)	1593 (1.5%)	1536 (1.8%)
Drug history in year before			
NSAIDs	11 813 (23.3%)	27 335 (26.1%)	25 393 (28.9%)
Hormone replacement therapy	2645 (5.2%)	4882 (4.6%)	3681 (4.2%)
Fracture history in year before			
Non-vertebral fracture	730 (1.4%)	1603 (1.5%)	1430 (1.6%)
Vertebral fracture	51 (0.1%)	151 (0.1%)	169 (0.2%)

Table 2. Incidence of fractures stratified by daily dose

Fracture site	Dose category					
	Low (n = 50 649)		Medium (n = 104 833)		High (n = 87 949)	
	Rate (per 100 person-years)	Adjusted relative rate (95% CI)	Rate (per 100 person-years)	Adjusted relative rate (95% CI)	Rate (per 100 person-years)	Adjusted relative rate (95% CI)
Non-vertebral	1.6	1.0	2.2	1.18 (1.11–1.26)	2.6	1.44 (1.34–1.54)
Forearm	0.4	1.0	0.4	0.99 (0.88–1.13)	0.4	1.00 (0.85–1.17)
Hip	0.2	1.0	0.4	1.62 (1.38–1.90)	0.5	2.21 (1.85–2.64)
Vertebral	0.1	1.0	0.4	1.54 (1.29–1.84)	0.6	2.83 (2.35–3.40)

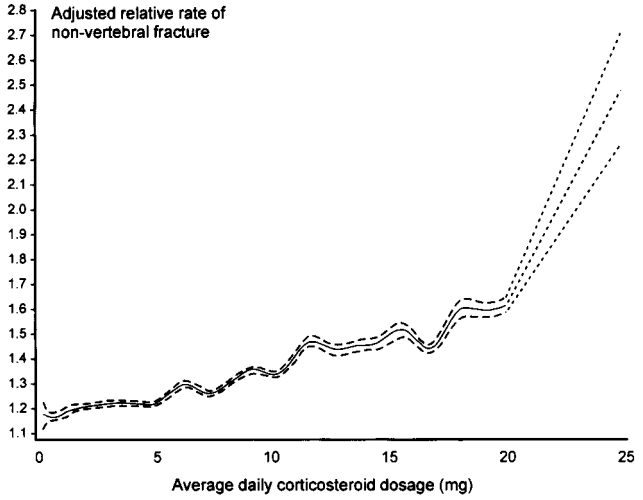

FIG. 1. Adjusted relative rate of non-vertebral fracture (dashed lines show 95% CI) according to continuous daily dose of corticosteroids (doses equivalent to prednisolone in mg). Estimates of risk become less stable above daily doses of prednisolone 20 mg.

Figure 1 shows the relative rate of non-vertebral fractures according to average daily corticosteroid dose compared with the control rates. The excess risk of fracture in the oral corticosteroid group was stable at around 20% for daily doses lower than 5 mg prednisolone or equivalent but increased for higher doses. Patients with a daily dose of 20 mg prednisolone or equivalent had a non-vertebral fracture rate which was about 60% higher than the rate in the control group.

We also evaluated the relationship of the risk of fracture to cumulative corticosteroid dose. Figure 2 shows that patients using a cumulative dose of less than 0.5 g prednisolone experienced a non-vertebral fracture relative rate of 1.8, while patients who had consumed a total of 10 g prednisolone or more had a rate of 2.7. The incidence of non-vertebral fracture decreased abruptly after cessation of oral corticosteroids irrespective of the prior cumulative dose. Similar patterns of increasing risk of fracture with higher cumulative dose and of decreasing rates after cessation of oral corticosteroid therapy were observed for hip and vertebral fractures.

In order to evaluate whether the risk of fractures was more closely related to the daily dose or the cumulative dose, the relative rate of non-vertebral fractures with increasing cumulative dose was estimated separately for each of the three daily dose groups (high, medium and low). As shown in Fig. 3, the relative rate of non-vertebral fractures was related more strongly to daily dose than to cumulative dose. The adjusted relative rate of non-vertebral fractures in the highest daily dose category only changed marginally (from a relative rate of 1.45 to 1.70) from the lowest (<0.5 g) to the highest (≥ 10 g) cumulative dose group. Similar results were found when we excluded oral corticosteroid users with a follow-up of less than 6 months from the analysis.

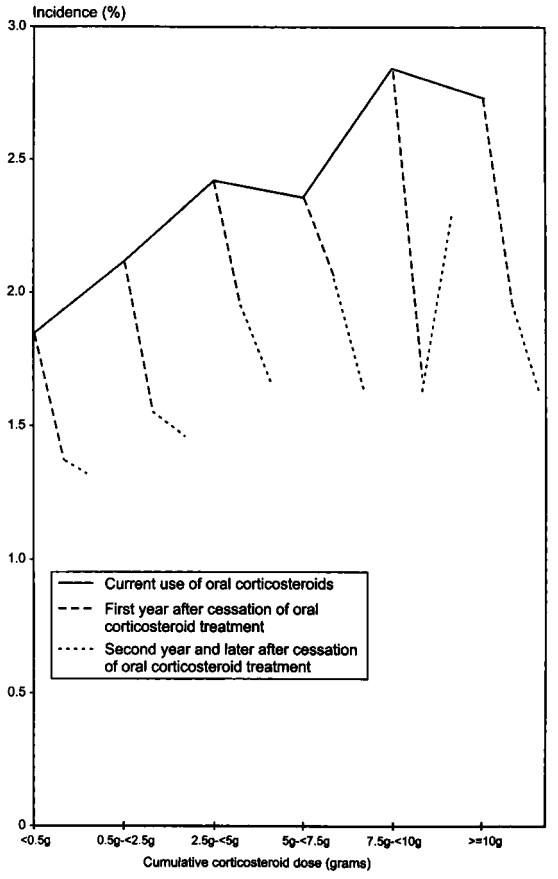

FIG. 2. Rate of non-vertebral fractures according to cumulative corticosteroid dose (in g of prednisolone or equivalent).

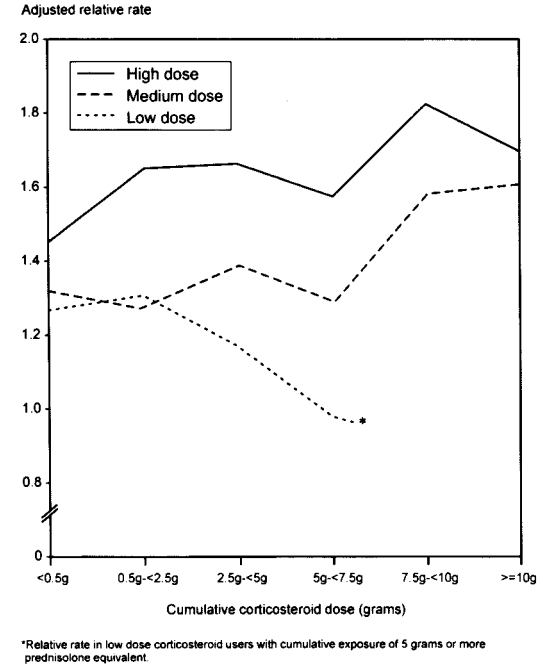

FIG. 3. Relative rate of non-vertebral fractures according to daily and cumulative doses of oral corticosteroids (prednisolone or equivalent).

In the highest daily dose category, the adjusted relative rate of non-vertebral fractures compared with the control group was 1.80 in the lowest (<0.5 g) and 1.71 in the highest (≥10 g) cumulative dose group.

Discussion

The results of this study suggest that the increased risk of fracture observed in patients using oral corticosteroids is strongly related to the daily corticosteroid dose. The risk of both hip and vertebral fractures was approximately doubled in patients using high daily doses (≥7.5 mg prednisolone or equivalent) compared with those using low doses (<2.5 mg prednisolone or equivalent). A monotonic relationship was observed between daily oral corticosteroid dose and the risk of fractures, without any apparent dose threshold. The risk of corticosteroid-induced fractures was found to be more strongly related to daily dose than to cumulative dose.

Although many studies have examined changes in bone density among patients using oral corticosteroids, the clinically more important end-point of fracture has been investigated less frequently, and in studies generally lacking statistical power [3–18]. Studies with fractures rather than bone density as the end-point may be important, given the observation that fractures in oral corticosteroid users occur in the presence of higher bone density than is the case for patients with involutional osteoporosis [3]. A previous study using this data set revealed that the risk of fractures increased soon after the commencement of oral corticosteroid therapy [19]; if this increased risk was mediated exclusively through bone density changes, an induction period of several months would be expected. Only two fracture studies, both conducted in patients with rheumatoid arthritis, specifically addressed the relationship of dose to the risk of fracture [5, 14]. A study of 52 oral corticosteroid users showed no correlation between cumulative dose and the prevalence of vertebral deformities [5]. In contrast, Dykman *et al*. [14] reported on 93 patients in whom a significant correlation was observed between cumulative corticosteroid dose, but not daily dose, and the risk of fracture.

In our study, a strong relationship was observed between daily corticosteroid dose and the risk of fracture, with higher risk in people using higher doses. The existence of a threshold corticosteroid dose above which the risk of fracture rises is contentious; if confirmed, such a threshold would be important in guiding preventive strategies. Some investigators have concluded that even low doses of oral corticosteroids have adverse effects on the skeleton, while others suggest a threshold daily dose of 7.5 mg prednisolone or equivalent [36–40]. Data pertaining to a threshold dose are difficult to interpret, as they are derived largely from pooled results of studies based on bone density rather than from single dose–response studies (using fracture as an outcome). We observed a monotonic relationship between oral corticosteroid dose and fracture risk without any evidence of a definite threshold. However, increases in fracture risk appeared to be smaller at daily doses less than 5 mg/day compared with higher doses. Selection bias may partly explain these small fracture risk increases at the lowest doses. Patients using less than 2.5 mg daily did not have increased fracture rates when compared with their own baseline rates [19]. The large increase in the risk of fracture observed with higher oral corticosteroid doses is less likely to be explained by such selection bias, as baseline differences were generally small.

We found that the risk of corticosteroid-related fractures was more strongly related to daily dose than to cumulative dose. The observed increase in risk among people with higher cumulative exposure largely disappeared after adjustment for daily dose, age, gender and other confounding variables. This contrasts with one previous report, which emphasized the relationship of fractures to cumulative dose rather than to daily dose [14]. The discrepancy may be related to differences in exposure ascertainment, as our study used prescription data whereas the study by Dykman *et al*. [14] employed patient interviews to determine exposure. The importance of daily dose is supported by our finding that fracture risks reverted towards baseline levels irrespective of prior cumulative dose level after the cessation of oral corticosteroid treatment. Several agents are now licensed for the prevention and treatment of corticosteroid-induced osteoporosis, and our findings suggest that they are most appropriately used during oral corticosteroid therapy, especially during periods when high daily doses are being used.

We assessed the validity of fracture ascertainment in this data resource by sending a questionnaire to the GPs of 150 randomly selected patients with a hip fracture and 150 patients with a vertebral fracture [41]. The results suggested that only a small proportion of cases (less than 15%) were not confirmed by either the GP or a diagnostic radiology report. This proportion was similar in the control population and the population taking oral corticosteroids, for both vertebral and hip fractures. Furthermore, the rates of hospitalization and death among fracture cases were similar between the comparison groups. These data suggest that the misclassification of cases was non-differential and was of similar magnitude in each group. Such misclassification would tend to underestimate the risk of fracture associated with oral corticosteroid therapy. There is an added problem in the diagnosis of vertebral fracture, which was primarily based on clinical and radiographic assessments. We did not have access to standardized radiographic morphometry, and we recognize that only a minority of all vertebral deformities come to medical attention and are clinically diagnosed [42]. Again, this misclassification by us was non-differential and would tend to further bias fracture estimates towards unity.

There are several difficulties in studying the association between oral corticosteroid use and the risk of

fracture in the setting of routine clinical practice, including biases due to selection, ascertainment and confounding. One important limitation specific to our analysis concerns the characterization of daily dose. As the prescribed daily dose was not recorded systematically by the GPs, the daily dose was averaged over the period between the first and last oral corticosteroid prescriptions. For patients using oral corticosteroids intermittently, this period included periods without treatment. This may have resulted in an underestimate of the excess fracture risk but also an underestimate of the daily dose. It was found that low-dose users were often using oral corticosteroids intermittently during follow-up whereas high-dose users were taking them more frequently in single treatment courses. The assessment of cumulative dose was not based on lifetime data but on a window of patient observation averaging around 5 yr (the time between practice enrolment and the end of the study). A Kaplan–Meier survival analysis of the duration of oral corticosteroid use indicated that the number of patients in actual clinical practice with high cumulative exposure is likely to be small. Another limitation concerns the possible role of underlying disease in the causation of fractures. We have reported previously that the relative rate of fracture in oral corticosteroid users compared with controls was similar in patient groups with different underlying diseases (chronic obstructive pulmonary disease, skin conditions, arthropathies, peripheral nervous disorders, and non-infectious enteritis and colitis) [41].

In conclusion, our data provide evidence that the risk of corticosteroid-induced fractures is more strongly related to daily dose than to cumulative dose. A monotonic relationship was observed between daily oral corticosteroid dose and the risk of fracture, without any definite dose threshold. These findings suggest that the adverse skeletal effects of oral corticosteroids are acute rather than chronic, and are related to the daily dose.

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