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A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids

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Summary

Background: Previous analyses of risk factors for glucocorticoid (GC)-induced osteoporosis have focused on the estimation of relative rather than absolute fracture probability.
Aim: To estimate risk scores for the individual probability of fracture in GC users.
Design: Retrospective data analysis.
Methods: We evaluated all patients aged 40 years or older with a prescription for oral GCs in the General Practice Research Database (GPRD), which comprises the computerized medical records of around 7 million UK subjects. Individual risk factors for osteoporotic fractures were identified, and combined in a predictive model for 10-year absolute fracture risk.
Results: Of 191 752 oral GC users aged $\geqslant$ 40 years, 7412 experienced an osteoporotic fracture. Several characteristics independently contributed to the fracture risk score (GC therapy, age, gender, fall history, fracture history, body mass index, smoking, previous diagnoses, use of medication, recent hospitalization and indication for GC treatment). Scores of 30, 40 and 50 corresponded to absolute 5-year fracture risks of 6.2%, 15.3% and 35.2%, respectively. A woman aged 65 years with RA, low BMI, and a previous history of fracture and falls, who used 15 mg GC daily (total risk score 54) would have a 5-year fracture risk of 47% (a man with similar history, 30.1%). Short-term use of high-dose GC therapy ($\geqslant$30 mg) was associated with only a small increased risk of osteoporotic fracture (RR 1.21, 95%CI 1.04–1.42) in patients with a history of GC use.
Discussion: This risk score helps to predict an individual's risk of fracture during GC use. Decisions about bone protection treatment could be based on long-term risks of fracture.

Introduction

Oral glucocorticoids (GCs), also known as oral corticosteroids, are potent anti-inflammatory agents, and are widely used for the treatment of a variety of inflammatory and allergic disorders, such as rheumatoid arthritis or asthma. GC-induced osteoporosis was identified more than 60 years ago, when Cushing first described the tendency of patients with excess endogenous GC to develop fractures.[1] Therapy with oral GC can lead to rapid loss of bone mineral density (BMD) and to an increased

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risk of fracture. A large epidemiological study reported dose-related increased rates of fracture in GC users,[2,3] with similar findings in several smaller studies.[4–8] Guidelines for its prevention and therapy of GC-induced osteoporosis have now been developed.[9,10]

The epidemiological information on the risks of fracture in oral GC users now concern relative risks (RR) of fracture, comparing the rate of fracture in GC users to that of control patients. There is limited information available to calculate the absolute fracture risk of an individual, specific for their age, sex and GC dose. Further, the relative contributions of GC use, bone-related risk factors such as fracture history, and extraskeletal risk factors such as the risk for falls, remain uncertain. In cardiovascular medicine, risk scores have been successfully developed to predict the long-term outcome of coronary heart disease in individuals. Thus, information on age, sex, serum cholesterol, blood pressure and other clinical characteristics can be used to estimate the absolute 5-year risk of death from cardiovascular disease.[11] Active intervention is then only considered for patients whose long-term risk is above a certain threshold. It has been proposed that treatment decisions should be based primarily on absolute long-term risks of fracture, rather than on relative risks.[12,13] The primary objective of this study was to estimate the long-term risks of fracture in patients using oral GCs by developing a predictive model.

Methods

Information for the study was obtained from the General Practice Research Database (GPRD), which comprises the computerized medical records of general practitioners. General practitioners (GP) play a key role in the UK health care system, as they are responsible for primary health care and specialist referrals. Patients are semi-permanently affiliated to a practice, which centralizes the medical information from the GPs, specialist referrals and hospitalizations. The data recorded in the GPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes.[14]

Study population

Details of the methods used in the investigation and of the overall fracture rates (relative to a control group of non-users) are available elsewhere.[2,3] The study population consisted of all patients aged 40 years or older with a prescription for oral GCs during the period of GPRD data collection. They were followed from the first GC prescription at age 40 years or older to the end of GPRD data collection (GPRD data collection started in 1987 and ended, for this study, in December 1997). The total follow-up period for each study patient was classified into periods of current and past GC exposure. As a patient's use of oral GCs could change over time, patients could move between these exposure periods over time. Each current exposure period started at the date of the prescribing of an oral GC; the duration of this current exposure period was based on the expected duration of GC use plus 3 months. In case of a repeat GC prescription within a current exposure period, this period was extended with the duration of use of the repeat prescription plus 3 months. In case of overlap between two prescriptions (i.e., a repeat prescription given within the duration of use for a previous prescription), the 'overlap' days were added to that of the repeat prescription. The maximum period of current exposure following a GC prescription was set at 6 months. Daily and prior cumulative GC dose were assessed at the start of each current exposure period. The daily dose of each GC prescription was based on the prescribed daily dose by the GP, as obtained from the written dosage instructions in the medical records. Using this daily dose and the information on the total amount of GC prescribed to the patient, the expected duration of GC use was estimated. In case of missing data, the median expected duration of use (based on data from patients of similar age and sex) was used. The period of past exposure was the time period from GC discontinuation (end of current exposure period) up to a new oral GC prescription or up to the end of data collection (whichever end-point came first). The past-exposure period was divided into periods of 6 months.

Cases were patients who had a clinical osteoporotic fracture during follow-up. These were defined as fractures that occurred at one of the following sites: radius/ulna, humerus, rib, femur/hip, pelvis or vertebrae. An earlier validation study found that the vertebral fractures as recorded in GPRD mostly concerned vertebral fractures that were clinically symptomatic and were confirmed radiographically.[15] Systematic morphometry of vertebral fractures was not routinely done by the GP. The history of any type of fracture prior to the first GC prescription was determined. Also, the occurrence of osteoporotic fracture at any other site during follow-up was noted. In order to exclude fractures that occurred at the same time but were recorded at a different time in the medical record, any fractures that occurred in the prior 3 months period were not included.

The other risk factors considered in the study included a recorded history of falls in the previous 6 months. The body mass index (BMI) and smoking history recorded around the time of the first GC prescription were also assessed, where available. The analysis also evaluated the number of risk factors, based on the presence of diseases and drugs that have been associated with an increased risk of fracture in a previous GPRD study.[16] These included a history of anaemia, dementia, and cerebrovascular disease, or prescriptions in the previous 6 months for anticonvulsants, antiarrythmics, hypnotics/anxiolytics, antidepressants, or anti-Parkinsonian drugs. Information on risk factors was collected at the date of each GC prescription or at the date of starting each 6-monthly period of past exposure.

The indication for GC treatment was based on the illnesses recorded in the medical records in the period of time from 6 months before the first prescription up to the last GC prescription. The following diseases were noted: respiratory disease (ICD9 490–496), rheumatoid arthritis (RA) (714), polymyalgia rheumatica (725), other connective tissue disorders (710–713, 715–719), non-infectious enteritis and colitis (555–558), dermatitis (692), other inflammatory skin disorders (690, 691, 693–698), urticaria (708), facial nerve disorders (351), other peripheral nervous system disorders (350, 352–359) and polyarteritis (446). Hospitalization for any of the diseases indicated for GC treatment in the 12 months before was also measured. Risk factors were included as categorical variables (present vs. absent). With respect to the fracture risks in different GC indications, patients were classified according to GC indication, and each indication was then compared to patients with respiratory disease.

Statistical methods

Cox proportional hazards models were used to estimate the long-term risks of fracture. For each set of patient characteristics, the Cox model allows calculation of an individual's probability of fracture (i.e. survivor function). We first fitted regression models with daily and cumulative GC exposure (square-root-transformed) and an interaction term between daily and cumulative GC exposure. Past GC exposure was considered the reference category. We additionally investigated models with quadratic and cubic GC exposure variables, to address any non-linear relationship between GC exposure and fracture risk. Then regression models were fitted with the exposure variables, risk factors and the various GC indications. Backward regression used a significance level of 0.05. For age, sex, the risk factors and GC indications, we also investigated possible statistical interactions with GC exposure. Only the interaction with age was strong enough to merit inclusion into the final Cox model. The beta-coefficients of this Cox model (the exponentials of which constitute the RRs) were converted into integer risk scores. The value of each integer is the rounded sum of the predictors of the Cox model multiplied by 10. Because of the time-dependent exposure variables, the risk score of a patient was averaged over the total follow-up period. The 5-year risk of fracture was then estimated using these scores. This score represents the probability of fracturing, conditional on patient survival. The 10-year risk of fracture was based on extrapolating the 5-year risk; the average hazard rate was calculated (log of risk) and then applied over 10 years. Various methods were used to test the fitting of the Cox models.[17] This included the testing of the proportional hazards assumption. We also compared the observed 5-year probability of fracture (based on the Kaplan-Meier estimate) to the probability predicted by the Cox model. This was done by dividing the study population into 10 groups, based on the predicted probability of fracture. The observed and predicted probabilities for fracture were then compared.

An analysis was conducted estimating the long-term risks of fracture for populations with different underlying fracture rates. As vertebral fractures are under-diagnosed in GPRD,[15] we used the morphometric vertebral fracture rates from the European Prospective Osteoporosis Study (EPOS)[18] and compared them to the GPRD rates. The log of the ratio of these rates was added to the risk score. In effect, this analysis replaced the underlying baseline fracture rate of the GPRD with that from another population. The underlying assumption was that the effects of GC exposure and of risk factors are similar between the different populations (i.e. RRs of GC exposure are identical).

Validation of predictive model

We also validated the risk score in another dataset, The Health Improvement Network (THIN) Research Database, which contains computerized medical records of patients at general practices in the UK, similar to the GPRD. The study population consisted of all women aged 50 years or older who were registered at one of the THIN practices, and who were prescribed an oral GC after 1997. It included 33 330 women, with 1489 clinical osteoporotic fractures.

Results

The study population consisted of 191 752 patients who were aged ⩾40 years and prescribed an oral GC. The patients received a mean of 7.7 GC prescriptions (median 2). The total follow-up period (mean 2.5 years per person) was divided into periods of current and past GC exposure. About 59.5% of the total follow-up was classified as past exposure. There were 7412 patients with a clinical osteoporotic fracture (2144 hip and 1269 clinical vertebral fractures).

Table 1 shows the RRs of fracture for age, sex, risk factors and GC indication. Strong risk factors for fracture included age, sex, low BMI, fall and fracture history. Patients with RA had an increased risk of fractures, compared to those with respiratory disease. GC users with a low BMI and fall history had a five-fold increased risk of hip fracture (RR 5.37, 95%CI 2.38–12.09). For GC users with both fracture and fall history, the hip fracture risk was similarly increased (RR 5.40, 95%CI 3.61–8.08). The RRs for fracture stratified by daily and cumulative GC dose are shown in Table 2. Fracture risk was increased for all doses, with the exception of short-term use of GC at a daily dose <2.5 mg/day. In patients with higher daily dose (⩾30 mg/day) and low cumulative dose (⩽1 g), GCs were often used for only short periods of time (average GC duration 10 days). This intermittent high-dose GC therapy was associated with only a small increased risk of clinical osteoporotic fracture. The age- and sex-adjusted RR for fracture was 1.20 (95%CI 0.98–1.46) in first-time GC users and 1.21 (95%CI 1.04–1.42) in patients with a high dose of GC at least 3 months after the end of prior GC use. These figures were 2.38 (95%CI 1.52–3.73) and 1.50 (95%CI 0.97–2.31) for clinical vertebral fractures and 0.86 (95%CI 0.57–1.30) and 0.78 (95%CI 0.54–1.14) for hip fractures, respectively.

Table 3 shows the risk score for various patient characteristics, with an example calculation shown in Table 4. The 5-year risks for a clinical osteoporotic fracture for patients with total scores of 30, 40, and 50 were 6.2% (95%CI 6.0–6.4), 15.3% (95%CI 14.9–15.7), and 35.2% (95%CI 33.7–36.6%), respectively (Figure 1). The median risk score at start of GC therapy (excluding GC use) was 19 for women aged 40–49 years (75% percentile: 21) and 13 (15) for men of this age. These figures were 28 (31) for women and 22 (24) for men aged 60–69 years, and 37 (41) for women and 31 (32) for men aged 80–89 years.

Receiver operator characteristic (ROC) curves, which plot sensitivity (true positive rate) vs.

Table 1 Prevalence and the RR of fracture for age, sex, risk factors and indications for glucocorticoid (GC) use

Risk factor	Prevalence	Clinical osteoporotic fracture RR (95%CI)	Femur/hip fracture RR (95%CI)	Clinical vertebral fracture RR (95%CI)
Age (for each 10 years of age)	–	1.63 (1.60–1.66)	2.40 (2.30–2.50)	1.66 (1.58–1.74)
Sex, men	39.8%	0.51 (0.49–0.54)	0.51 (0.46–0.57)	0.65 (0.57–0.73)
*Body mass index**				
<20	4.8%	1.48 (1.34–1.62)	1.96 (1.66–2.32)	1.54 (1.22–1.93)
⩾26	43.5%	0.84 (0.78–0.89)	0.64 (0.55–0.74)	0.87 (0.74–1.02)
Smoker*	35.0%	1.16 (1.10–1.23)	1.27 (1.13–1.42)	1.14 (0.99–1.30)
History of fall in prior 6 months	1.6%	2.57 (2.30–2.86)	2.52 (2.12–3.00)	2.24 (1.71–2.92)
Fracture history	10.7%	1.92 (1.81–2.03)	1.68 (1.52–1.87)	2.04 (1.79–2.34)
Other osteoporotic fracture during follow-up	2.2%	–	1.90 (1.55–2.34)	2.22 (1.69–2.90)
Number of disease/drug risk factors				
1	23.8%	1.46 (1.39–1.54)	1.67 (1.52–1.84)	1.63 (1.44–1.84)
2+	8.6%	1.81 (1.69–1.94)	2.36 (2.10–2.66)	1.75 (1.47–2.08)
Indication for GC treatment				
Rheumatoid arthritis	8.1%	1.52 (1.39–1.66)	2.01 (1.72–2.35)	2.21 (1.84–2.65)
Polymyalgia rheumatica	11.0%	1.03 (0.95–1.11)	0.94 (0.82–1.08)	1.16 (0.98–1.37)
Non-infectious enteritis and colitis	7.1%	1.32 (1.20–1.44)	1.43 (1.20–1.70)	1.71 (1.41–2.08)
Respiratory disease	53.5%	Reference	Reference	Reference
Hospitalization for GC indication in year before	5.6%	1.83 (1.68–2.00)	1.84 (1.56–2.16)	3.52 (3.00–4.14)

RRs are adjusted for age and sex. *Information missing on body mass index for 34.5% of the patients and on smoking history for 20.2%.

Table 2 Prevalence and the RR (95%CI) of fracture during glucocorticoid (GC) exposure (compared to past GC exposure)

Daily GC dose* (mg/day)	Previous cumulative GC exposure (g)	Prevalence	Clinical osteoporotic fracture RR (95%CI)	Femur/hip fracture RR (95%CI)	Clinical vertebral fracture RR (95%CI)
<2.5	⩽1	3.3%	1.05 (0.70–1.59)	0.67 (0.28–1.62)	2.11 (0.87–5.10)
	>1	0.8%	1.41 (1.14–1.73)	1.04 (0.68–1.59)	3.22 (2.09–4.95)
2.5–4.9	⩽1	1.9%	1.67 (1.33–2.10)	1.47 (0.97–2.23)	2.60 (1.49–4.53)
	>1	8.6%	1.41 (1.23–1.62)	1.46 (1.15–1.85)	1.83 (1.26–2.66)
5–7.4	⩽1	8.3%	1.33 (1.17–1.52)	1.48 (1.18–1.85)	2.21 (1.62–3.03)
	>1	26.0%	1.81 (1.67–1.96)	1.64 (1.42–1.90)	3.99 (3.33–4.79)
7.5–14.9	⩽1	4.5%	1.95 (1.65–2.29)	2.25 (1.72–2.94)	3.36 (2.30–4.92)
	>1	16.9%	2.17 (1.97–2.39)	2.48 (2.11–2.91)	4.78 (3.88–5.88)
15–29.9	⩽1	6.3%	1.53 (1.32–1.78)	1.96 (1.54–2.51)	2.12 (1.44–3.13)
	>1	5.1%	2.84 (2.45–3.30)	2.62 (1.98–3.48)	8.89 (6.83–11.58)
⩾30	⩽1	15.3%	1.21 (1.08–1.35)	0.93 (0.73–1.18)	1.85 (1.39–2.46)
	1–5	2.1%	2.00 (1.52–2.63)	1.28 (0.67–2.48)	7.06 (4.54–10.98)
	>5	0.9%	3.63 (2.54–5.20)	3.13 (1.49–6.59)	14.42 (8.29–25.08)

Estimates for RR are based on categories of GC exposure, adjusted for age and sex. *Information missing on daily GC dose for 29.4% of the patients.

Table 3 Risk score of fracture for glucocorticoid (GC) exposure, age, sex, risk factors and indications for GC use

	Clinical osteoporotic fracture			Femur/hip fracture			Clinical vertebral fracture		
Age (years):	50	65	80	50	65	80	50	65	80
Daily 7.5 mg	8	6	5	12	8	4	15	14	12
Daily 15 mg	11	9	7	15	10	5	20	18	16
	All ages			All ages			All ages		
Age (for each 10 years of age)	4			8			4		
Male sex	−6			−6			−4		
Body mass index <20	3			6			3		
Body mass index ⩾26	−1			−4			−1		
Smoker	1			2			1		
History of fall in 6 months before	8			7			6		
Fracture history prior to GC use	6			5			7		
Other incident osteoporotic fracture during GC treatment	–			4			5		
Disease/drug risk factor (for each factor)	2			3			2		
Recent hospitalization for underlying GC indication	4			4			9		
Indication for oral GC treatment									
RA	1			4			3		
Non-infectious enteritis and colitis	1			2			3		

(1 – specificity) (false positive rate) and the areas under the ROC curve were estimated. For clinical osteoporotic fractures, the area under the ROC curve was 69.7%; for hip fracture, 78.1%; and for clinical vertebral fracture, 74.8%.

When applying the risk score as developed in GPRD to another dataset (THIN), the risk score equally differentiated between high- and low-risk patients (in the original GPRD population, the RR for an increase of 10 in the risk score was 2.63

Table 4 Example of risk score calculation for a man aged 65 years at start of 5 years use of 15 mg prednisone daily, and who had low BMI, fracture and fall history and rheumatoid arthritis

Parameter	Value	Clinical osteoporotic fracture	Femur/hip fracture	Clinical vertebral fracture
Age at midpoint of 5-year period	67.5 years	$6.75 \times 4 = 27$	$6.75 \times 8 = 54$	$6.75 \times 4 = 27$
GC dose	15 mg/day	9	10	18
Sex	Male	−6	−6	−4
BMI <20	Yes	3	6	3
Smoker	No	0	0	0
Past fall	Yes	8	7	6
Past fracture	Yes	6	5	7
RA	Yes	1	4	3
Total score		48	80	60

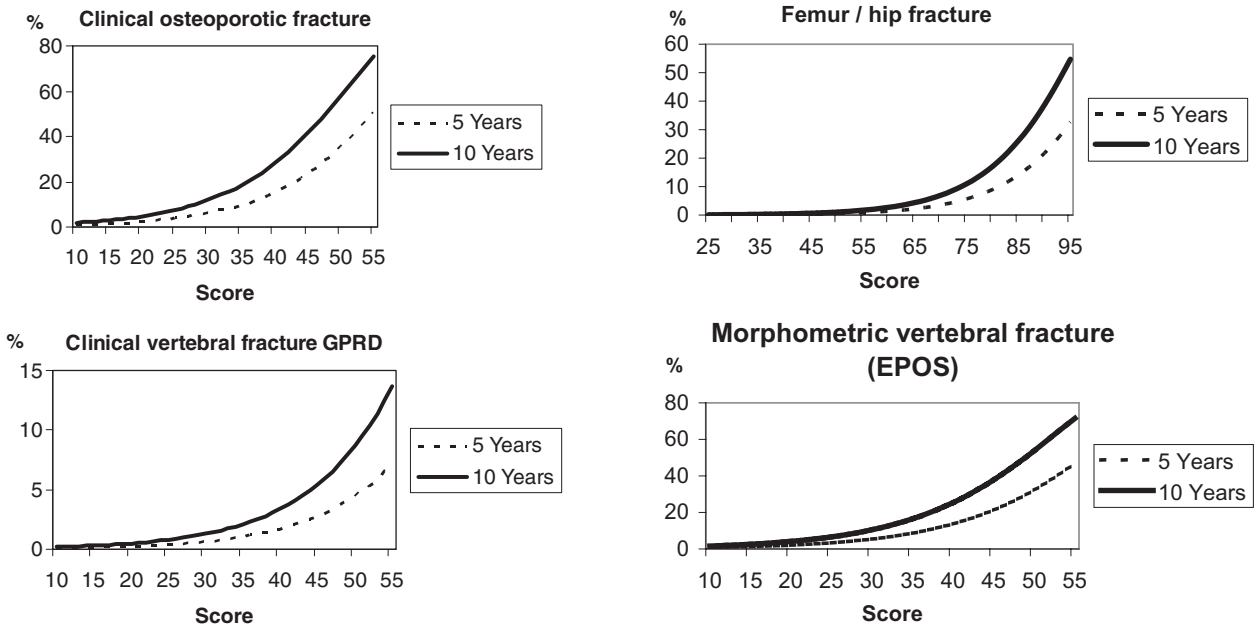

Figure 1. Relation between risk score and risk of fracture for 5- and 10-year periods

among elderly women; in THIN, it was 2.74). These figures were 2.60 and 2.48 for clinical vertebral fractures, and 2.64 and 2.58 for hip fractures, respectively.

Discussion

We have developed a risk score which provides an easily applicable method of estimating a patient's individual risk of fracture, based on routinely available clinical information. Our data suggest that the long-term risks of fracture can be substantial in GC users; for a woman aged 65 years using 7.5 mg prednisolone daily, there is a one in four likelihood of suffering a clinical osteoporotic fracture over 10 years.

The risk score as developed in this study allows calculation of the long-term risk of fracture in patients using oral GCs. As in cardiovascular medicine, such information on individual risks can be useful in identifying patients who require active intervention and monitoring. Current approaches of intervention thresholds based on (e.g.) age, may result in the over-treatment of elderly patients with below-average risks and under-treatment of younger patients with above-average risks. Further study is required to determine the threshold of individual risk at which intervention will become cost-effective in patients using oral GCs.

In postmenopausal osteoporosis, intervention thresholds are currently determined largely by assessment of BMD or a prior history of fracture. However, fracture probability varies substantially with age at any given level of BMD. Older people have much higher fracture risks than younger people, even when their BMDs are similar.[12] For GC users, there are even stronger grounds for using BMD as one of several risk indicators, rather than as the single determinant for intervention. There is growing evidence that the increased risk of fracture in GC users is not only related to a reduction in amount of bone (BMD), but also to the quality of bone. Preliminary results of an animal study indicated that bone quality (osteocyte viability) was an important determinant of bone strength, independent of BMD.[19] A meta-analysis showed that fractures occur at much higher rates in GC users than expected on the basis of BMD differences,[10] and in a comparison of GC users and non-users, GC users had considerably higher fracture risks than non-users at similar levels of BMD.[20] Several treatment guidelines now recommend that BMD is only measured in patients with an intermediate, and not high, risk of fracture. Further studies are warranted to examine the value of measuring BMD in this context.

In addition to the effects on bone quality, oral GC therapy may affect the risk of fracture through extraskeletal mechanisms. We found that patients on GC had an increased risk of falling,[4] and fall history contributed to our risk score. Although previous studies examining the relationship between GC use and fracture risk have not directly examined the frequency of falling, a British case-control study did suggest that GC users had increased levels of frailty, physical inactivity, and immobility.[21] And oral GC therapy may lead to muscle weakness. Thus, a history of falls (a well-documented risk factor for subsequent falls[22]), is also an important risk factor for fractures in oral GC users.

The daily dose in this study was based on the dosage prescribed by the general practitioner, and could therefore vary over time. In a previous study that was used to calculate RRs of fracture in the study population, the daily dose was derived from a single average (calculated from the total number of tablets prescribed and length of follow-up).[2,3] The use of a time-varying measure of exposure may be preferable. Recent research found that fracture risk increases rapidly in GC users and that daily, but not cumulative, GC dose is a strong predictor for incident fracture in GC users.[20] Nevertheless, two other studies have reported that cumulative GC dose was a stronger predictor of fracture than daily dose.[6,7] The main limitation of these two studies was their reliance on prevalent fracture: patients with high cumulative exposure will have more prevalent fractures even if the incidence of new cases is not increasing with larger cumulative dose, as their time on treatment and disease duration will be longer. Prevalence is a function of underlying incidence rate of fracture as well as of duration of therapy or disease. We believe that it is inappropriate to make inferences on the relative contributions of daily and cumulative dose on the basis of prevalent cases only.

The risk estimates in this study are based on historical data. It has been argued that such data can only be an estimate for prospective prediction of fracture risk, because populations and circumstances are continuously changing.[23] At the time of this study, the awareness of fracture as a side-effect of GC therapy was probably limited, as reflected by the low prevalence of use of bone-active medication.[24] This may have improved over time, with better information now available on skeletally protective diet or exercise. Also, the risk estimates in this study may not be generalized to other populations, as GC effects may vary. It would be more appropriate to view the risk estimates in this study as a tool to improve the prediction of GC-related fractures, rather than as definitive estimates applicable to every patient.

Our findings are based on a complex mathematical model. We evaluated the key underlying assumptions used, and its overall predictive capacity performed well. However, we did not evaluate all possible interactions between the risk factors and for certain risk factor combinations; the model may therefore have over- or under-estimated fracture risks. Another limitation was that we did not have information on all risk factors for fracture (such as BMD, exercise or diet), which would improve the accuracy of prediction for an individual patient. We also did not include in the model use of bone-protective medications, such as bisphosphonates and hormone replacement. Use of such medication prior to a fracture was infrequent in the study period,[24] and the estimates for the risk score did not vary substantially after excluding patients who used these drugs.

In conclusion, patients using GC may have a substantial absolute long-term risk of fracture. A simple risk score based on GC dose and indication, patient BMI, fracture and fall history, and history of other disease and concomitant drug use, can help to quantify this absolute individual risk. This score can also be used to target preventative or investigative action to patients with higher long-term risks.

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