RHEUMATOLOGY ADVANCES IN PRACTICE

Rheumatology Advances in Practice 2022;00:1–5
https://doi.org/10.1093/rap/rkab089
Advance Access Publication 16 November 2021

Concise report

Paradoxically protective effect of glucocorticoids on bone mass and fragility fracture in a large cohort: a cross-sectional study

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Abstract

Objectives. Glucocorticoids (GCs) increase the risk of fracture through reduction in BMD; they may also reduce bone quality, but recent supporting data are scarce. We aimed to confirm these effects in a large population-based cohort.

Methods. We used data from patients referred for first hip and lumbar spine BMD estimation by the sole DXA scanner in the north-west of England between June 2004 and September 2016. We compared the history of fractures and BMD between patients currently on GCs and patients never exposed to GC. A logistic model adjusted for possible confounders.

Results. More than 20 000 subjects were included, 82% female, with mean age 63 (S.D. 13) years; 19% were currently on GCs. The patients on GCs were more often male, with higher BMI, but their age was similar to those not exposed to GC. Surprisingly, patients receiving GCs had ~2% higher BMD at both sites ($P < 0.001$) and lower prevalence of (history of) fractures (22% *vs* 34%; $P < 0.001$). The corresponding odds ratio was 0.53 (95% CI: 0.49, 0.58); adjustment for age, sex, BMI and the number of indications for scanning did not alter the association.

Conclusion. In this large population-based cohort, current GC use compared with never use was associated with higher bone mass and fewer rather than more fractures after adjusting for confounders. These results might be subject to unmeasured confounding, but for now they do not lend support to a detrimental effect of GCs on bone.

Key words: glucocorticoids, bone mineral density, dual X-ray absorptiometry, epidemiology, modelling, fragility fractures, risk factors

CLINICAL SCIENCE

Key messages

- Data on the use of CSs in large populations are scarce.
- CSs appeared protective of BMD loss in this large observational cohort.
- Possible explanations include the indication for CSs and the possible confounding with inflammation.

Introduction

It is well known that glucocorticoids (GCs) can reduce BMD [1], and their use is also associated with an increased propensity to fracture [2–6, 7]. Fracture data have been derived mostly from epidemiological studies in cohorts of patients with RA.

The data on the relationship between BMD and fracture in GC-treated patients is conflicting, with some [1, 2, 7], but not all [6], suggesting that GCs affect bone

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Submitted 18 August 2021; accepted 1 November 2021

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quality, increasing the propensity to fracture at a given BMD. The last study dates from 2003 [7], which might not reflect the many changes in therapy that have occurred since then. A more recent systematic review [8] has also suggested that these patients are undertreated, which makes this area of study more important.

A recent meta-analysis on the prevalence of vertebral fractures amongst patients who have had chronic CS exposure has given an estimate of annual incidence of vertebral and no-vertebral fractures as 3.2% (95% CI: 1.8, 5.0) and 3.0% (95% CI: 0.8, 5.9), respectively [9].

We therefore set out to establish whether GCs are associated with fracture in a more recent cohort and to explore the relationship with BMD. We hypothesized that GC-treated patients would more frequently have a history of fracture and that, in patients with a fracture, those on GCs would have a higher BMD than those not on GC. We used the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines [10] for reporting observational studies.

Methods

The Royal Lancaster Infirmary, a district hospital in the north-west of England (Fig. 1), has had the sole DXA scanner, a lunar DPX (GE) machine, in the region since 1992. Patients are referred from primary and secondary care and have their bone density assessed in the lumbar spine (average of L1–L4) and the femoral neck. Information on the reason for referral to the DXA scanner was obtained from the referral. Data on risk factors for osteoporosis were also collected by questionnaire when the patient attended, in addition to demographics, including height and weight. Risk factors included whether they had sustained a self-reported fragility

FIG. 1 Map of England, showing the north-west in red

fracture, defined as a fracture from standing height or less, and other Fracture Risk Assessment Tool (FRAX) risk factors, including family history of fracture, smoking, alcohol, secondary osteoporosis as defined by type I (insulin-dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition or malabsorption and chronic liver disease. Data on height and weight were used to calculate BMI (in kilograms per square metre). Data on previous and current GC use were also routinely collected, although the duration of the treatment, indication for CSs and the dose were not recorded. Other co-morbidities were also collected. Data were then kept on a Microsoft access relational database until extracted for analysis. Full ethical approval for pseudonymised data extraction was obtained from the local ethics committee, NRES Committee North West Preston (project number 14/NW/1136).

Statistical analysis

All patients referred for their first scan between June 2004 and September 2016 were eligible. These scans were all done on a single GE Lunar DPX machine. Patients on GCs at the time of scanning were identified and formed the exposed group; patients with previous exposure to GCs were excluded from the analysis. All other patients were used as comparators. Normality was assessed using estimates of skewness and kurtosis [11] Initially, differences between the groups exposed and not exposed to GC were explored with χ^2 and Student's unpaired *t*-tests (see Table 1). Logistic models where then fitted to study the odds of fracture before and after adjustment for possible confounders, including BMD, biological sex, BMI and the number of FRAX indications for scanning, as above. Lumbar spine and hip BMD were also modelled separately, because the FRAX tool (www.sheffield.ac.uk/FRAX) uses the BMD in the hip as the best predictor of fracture. All analyses were done in STATA v.12 www.stata.com STATA Corp., TX, USA.. Forward stepwise models were then fitted to examine the variables that would be associated with fracture in this cohort, with a probability of removal set at a *P*-value of >0.10 and probability of entry at $P < 0.05$.

To study the effect of bone-preserving treatment, we also ran the above analyses in patients not on bisphosphonates, and also in patients not on bisphosphonates, calcium or vitamin D. Additionally, we carried out a sensitivity analysis restricted to women only and used age at menopause as a continuous variable; this did not alter the results (data not shown).

Results

A total of 20 239 subjects were included in the study. Compared with non-exposed subjects, the group currently on GCs were more often male and, correspondingly, were slightly taller and heavier (Table 1). Unexpectedly, the exposed group had a significantly higher BMD in the lumbar spine and femoral neck and significantly less history of fragility fractures (22% *vs* 34%, $P < 0.001$). The unexposed patients had a higher number of indications for scanning. Logistic modelling (Table 2) adjusted for confounders including BMD and indications for scanning confirmed the relationship.

In the sensitivity analyses (Supplementary Tables S1 and S2, available at *Rheumatology Advances in Practice* online), we looked at patients not on bisphosphonate treatment at the time of the scan ($n = 17\,367$), of whom 2762 (16%) had sustained a fracture (Supplementary Table S1 available at *Rheumatology Advances in Practice* online); and at patients not on bisphosphonates, calcium or vitamin D ($n = 16\,949$), of whom 4996

Table 1 Characteristics of the whole cohort and differences between those currently on and those never exposed to glucocorticoids

Characteristic	All, $n = 20\,239$	Currently on GC, $n = 3821$	Not exposed, $n = 16\,418$	Difference, *P*-value
Females, %	82	65	86	<0.001
Age at scan, years	63 (13)	63 (13)	63 (14)	0.26
Height, cm	162 (88)	163 (10)	162 (8)	<0.001
Weight, kg	71 (16)	74 (17)	70 (15)	<0.001
BMI, kg/m^2	27 (24)	28 (43)	27 (18)	0.004
BMD, g/cm^2				
L1–L4	1.07 (0.20)	1.09 (0.20)	1.06(0.20)	<0.001
Femoral neck	0.91 (0.16)	0.93 (0.17)	0.90 (0.16)	<0.001
History of fracture, %	32	22	34	<0.001
Number of other indications for scanning, median (inner quartiles)	1 (0, 1), range 0–5	0 (0, 1)	1 (0, 1)	<0.001

Values are the mean (S.D.) unless otherwise noted. GC: glucocorticoid.

TABLE 2 Result of the logistic regression examining the propensity to fracture on CSs, unadjusted and adjusted for possible confounders ($n = 20\,239$)

	Odds ratio	95% CI
Unadjusted	0.53	0.49, 0.58
Adjusted for:		
Biological sex	0.55	0.50, 0.60
Biological sex; age	0.54	0.50, 0.59
Biological sex; age; BMI	0.54	0.49, 0.58
Biological sex; age; BMI; indications for scanning	0.56	0.51, 0.61
Biological sex; age; BMI; indications for scanning; lumbar spine BMD	0.54	0.49, 0.58
Biological sex; age; BMI; indications for scanning; femoral BMD	0.53	0.48, 0.58

(30%) had sustained a fracture (Supplementary Table S2, available at *Rheumatology Advances in Practice* online). Odds ratios were similar to those found in the main analysis.

Discussion

In a large dataset of patients referred for first bone scan, we set out to confirm the hypothesis of van Staa *et al.* [7] that patients on GCs have higher bone fragility, as evidenced by more frequent fractures occurring at higher bone density levels than patients with senility fractures. To our surprise, we found that patients currently on GCs had somewhat higher BMD and substantially fewer fragility fractures than patients never exposed to GC.

The strengths of the study include its size, the routine and single point of medical care setting, and the cross-sectional design, in which data for all patients were available in the same standardized way.

The weaknesses of the study include that, unfortunately, the indication, dose and duration of GC treatment were unknown. We also did not control adequately for the indication for referral for scanning, other than the risk factors. There could be a hypothetical cohort of patients on CSs with prevalent fractures who would have not been referred, skewing the estimate. Additionally, patients referred could have primary care practitioners who would be much more likely to intervene in the bone health of this population, which could also skew the results.

In the analysis adjusted for all measured potential confounders and the analyses in untreated subgroups, the effect was unaltered. This makes it unlikely that differences between the groups in demographics, concomitant disease or therapy caused this effect.

One hypothesis is that CSs could exert this effect through their potent anti-inflammatory effect [12] and therefore their usual influence on bone cells [13] could be altered.

In theory, the difference in bone mass and prevalent fractures could be caused by (unmeasured) selection bias, whereby physicians routinely refer patients with suspected senile osteoporosis regardless of fracture but refrain from doing so in GC-treated patients who have sustained a fracture. However, this selection bias would have to be substantial.

We accept that the limitations of this study should be taken into account, but we argue that in such a large cohort, this finding is of substantial interest and would be worthy of comment.

Our data are in contrast to those seen in a Bayesian meta-analysis of studies [9], which showed an increase in fractures in patients on GCs; nonetheless, despite the limitations this is an unexpected finding.

If we accept the findings as true, a possible explanation might be the low doses used in general practice and the anti-inflammatory effect of GC counteracting its intrinsic detrimental effects on bone.

In conclusion, this retrospective cohort study covering all patients from a large region does not support a large role for current GC use in bone loss and fragility fracture.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: M.B. has been sponsored to attend regional, national and international meetings by UCB Celltech, Roche/Chugai, Pfizer, Abbvie, Merck, Mennarini, Janssen, Bristol-Myers Squib, Novartis and Eli Lilly. He has received honoraria for speaking and attended advisory boards with Bristol-Myers Squib, UCB Celltech, Roche/Chugai, Pfizer, Abbvie, Merck, Mennarini, Sanofi-Aventis, Eli-Lilly, Janssen, Amgen, Novartis and Gilead. He has received honoraria from educational groups Revalidaid and TREG consultants. The remaining authors have declared no conflicts of interest.

Data availability statement

Data are available upon request.

Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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