RHEUMATOLOGY ADVANCES IN PRACTICE

Letter to the Editor (Matters arising from published papers)

Rheumatology Advances in Practice 2022;00:1–2
http://doi.org/10.1093/rap/rkac010
Advance Access Publication 17 February 2022

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

Dear Editor, We read with interest the report by Bukhari *et al.* [1], entitled: 'Paradoxically protective effect of glucocorticoids on bone mass and fragility fracture in a large cohort: a cross-sectional study'. This single-centre study compared patients with and without glucocorticoid (GC) treatment who were referred for DXA. The authors conclude that current GC use, compared with never-use, was associated with higher bone mineral density (BMD) and fewer fractures, and thus results do not support the notion that GCs are detrimental to bone.

The concluding statements by the authors are controversial, because the vast majority of preclinical models, trials and observational studies show that GC treatment results in increased fracture risk by a multitude of mechanisms, including BMD loss [2–4]. In our opinion, the unexpected outcomes found by Bukhari *et al.* [1] are likely to be attributable to the use of a cross-sectional study design, which does not assess temporality and is subject to substantial bias. Although the authors briefly mention the potential for selection bias, we believe the mechanisms that might have led to the perceived protective effects of GCs deserve greater attention.

First, GC exposure is likely to influence the likelihood of, and serve as the rationale for, receiving a DXA scan. In contrast, non-GC users typically are referred for DXA because they present with classic osteoporosis risk factors (e.g. older age, prior fracture, multiple fracture risk factors or recent height loss). Thus, DXA scan is a downstream consequence (effect) of both GC exposure and fractures (Fig. 1). Selection bias arises owing to conditioning on this common effect in a cross-sectional study [5]. Given that control patients must have had a DXA scan, a patient with a DXA scan but without GC exposure is more likely to have another cause for referral, such as a prior osteoporotic fracture. GC exposure and fractures are therefore inversely related, and the association between GC use and lower risk of fractures is not likely to be a causal relationship, but selection bias.

Second, exacerbating this selection bias further, patients on GCs with a prior fracture are recommended to initiate therapy to prevent fractures without a DXA scan [6]. Many guidelines do not recommend DXA scans for these patients because they are already at high fracture risk regardless of their BMD and because BMD is less correlated with fracture risk among patients on GC therapy than for primary osteoporosis [3]. Patients with GC use and prior fractures are therefore even less likely to undergo a DXA scan than other patients.

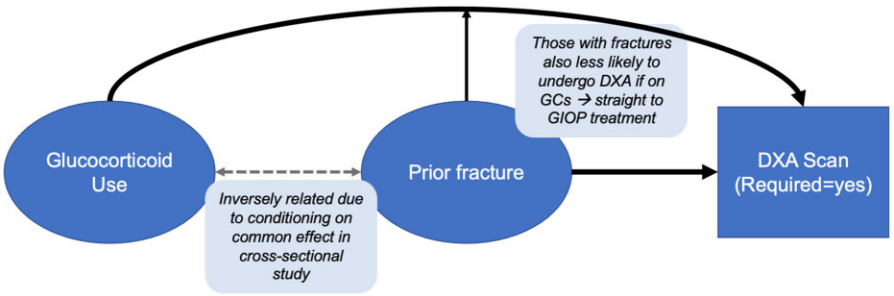
Furthermore, the detrimental effects of chronic GC use on bone health are often overlooked in clinical practice, particularly when a patient has many other competing co-morbidities and issues [7]. Patients on GC therapy who are referred to have a DXA scan (and are inherently less likely to have fractures, as discussed above) might have higher-quality care and better general health than those who are never referred. Indeed, patients under specialty care by a rheumatologist are twice as likely to be referred for a DXA scan within 6 months of chronic GC treatment (as recommended by the ACR guidelines [8]) *vs* patients with similar characteristics who are under the care of general practitioners [7]. Likewise, patients at a high risk for fracture with less urgent need for GC therapy (e.g. RA managed with DMARDs) might be less likely to receive GCs owing to their known effects on bone. These selection biases could contribute further to the GC group being inherently healthier and at a lower risk for both fracture and low BMD than other patients referred for DXA.

Third and finally, the authors hypothesize that suppression of inflammation might counteract the inflammatory cytokine-driven rapid bone loss in inflammatory diseases. However, given that no data are available on GC dose, start date or duration of use, the DXA referral might have occurred near the initiation of GC treatment, because it serves as a clinical guidance for necessity of bone-protective medication. In this case, those with GCs might be referred for a DXA scan as a preventative measure, and DXA results would not provide any information on the negative (or beneficial) effects of GC use on BMD and bone quality.

Even a longitudinal study design with statistical adjustment might not be able to correct for the selection biases inherent in observational studies examining potential protective effects of GCs on bone. Fortunately, a randomized controlled trial is underway to examine the effects of low-dose prednisone on outcomes in patients with RA, including BMD changes (NCT02585258).

To conclude, although the study includes a large population and use of a detailed patient questionnaire with fracture risk factor information, we believe the

Fig. 1 Directed acyclic graph illustrating potential for selection bias



GC: glucocorticoid; GIOP: glucocorticoid-induced osteoporosis.

contradictory findings are attributable more to crucial limitations in the study design and inherent selection bias than a causal relationship.

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: The authors have declared no conflicts of interest.

Data availability statement

Anonymized data are available from the authors on request.

Kaleen N. Hayes [1], Andrea M. Burden [2], Elizabeth M. Winter[3] and Barbara Hauser [4,5]

[1]Department of Health Services, Policy and Practice, Brown University School of Public Health, Providence, RI, USA, [2]Institute of Pharmaceutical Sciences, Department of Chemistry and Applied Biosciences, ETH Zurich, Zurich, Switzerland, [3]Center for Bone Quality, Division of Endocrinology, Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands, [4]Rheumatic Disease Unit, Western General Hospital, NHS Lothian and [5]Rheumatology and Bone Disease Unit, Centre for Genomic and Experimental Medicine Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK

Accepted 7 February 2022

Correspondence to: Barbara Hauser, Rheumatic Disease Unit, Western General Hospital, NHS Lothian, Edinburgh, UK, Crewe Road South, Edinburgh EH4 2XU, UK.
E-mail: barbara.hauser@igmm.ed.ac.uk

References

1 Bukhari M, Goodson N, Boers M. Paradoxically protective effect of glucocorticoids on bone mass and fragility fracture in a large cohort: a cross-sectional study. Rheumatol Adv Pract 2021;http://doi.org/10.1093/rap/rkab089.

2 Amiche MA, Albaum JM, Tadrous M *et al.* Fracture risk in oral glucocorticoid users: a Bayesian meta-regression leveraging control arms of osteoporosis clinical trials. Osteoporos Int 2016;27:1709–18.

3 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.

4 Hayes KN, Baschant U, Hauser B, Burden AM, Winter EM. When to start and stop bone-protecting medication for preventing glucocorticoid-induced osteoporosis. Front Endocrinol (Lausanne) 2021;12:782118.

5 Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology 2004;15:615–25.

6 Compston J, Cooper A, Cooper C *et al.*; The National Osteoporosis Guideline Group (NOGG). UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos 2017;12:43.

7 Majumdar SR, Lix LM, Yogendran M *et al.* Population-based trends in osteoporosis management after new initiations of long-term systemic glucocorticoids (1998–2008). J Clin Endocrinol Metab 2012;97:1236–42.

8 Buckley L, Guyatt G, Fink HA *et al.* 2017 American College of Rheumatology Guideline for the prevention and treatment of glucocorticoid-induced osteoporosis: ACR guideline for glucocorticoid-induced osteoporosis prevention and treatment. Arthritis Rheumatol 2017;69:1521–37.