EnM
ENDOCRINOLOGY AND METABOLISM

Editorial

Endocrinol Metab 2020;35:549-551
https://doi.org/10.3803/EnM.2020.308
pISSN 2093-596X · eISSN 2093-5978

Why Do We Need Proactive Management for Fracture Prevention in Long-Term Glucocorticoid Users?

Han Seok Choi

Division of Endocrinology and Metabolism, Department of Internal Medicine, Dongguk University Ilsan Hospital, Dongguk University College of Medicine, Goyang, Korea

Glucocorticoids are steroid hormones that play an important role in several immunological and metabolic processes. Cortisol, the most important endogenous glucocorticoid, was isolated from adrenal extracts in 1946 and synthesized later that year [1]. After the therapeutic potential of glucocorticoids as strong anti-inflammatory drugs was discovered, a variety of synthetic glucocorticoids that differ in both pharmacokinetics and pharmacodynamics have been developed and used for the treatment of various inflammatory, allergic, and autoimmune diseases. It is estimated that about 1% of the general population receives systemic glucocorticoids [2,3].

However, chronic use of glucocorticoids can lead to several adverse effects, including osteoporosis and fractures. The deleterious effects of glucocorticoids on bone occur in a biphasic pattern, with rapid bone loss in the first few months, followed by slow but steady loss of bone with continuous use. The mechanism underlying glucocorticoid-induced osteoporosis is predominantly characterized by reduced bone formation, along with a transient early increase in bone resorption [4]. The influence of glucocorticoids on bone formation is mediated by direct inhibition of osteoblast proliferation and differentiation, as well as by increasing apoptosis of mature osteoblasts and osteocytes. Glucocorticoids can also directly stimulate osteoclast proliferation and activity, leading to increased bone resorption. Other indirect mechanisms, including hypogonadism, reduced muscle mass, and renal and intestinal loss of calcium, also contribute to bone loss and fragility associated with long-term glucocorticoid use [4].

Osteoporosis has become one of the most common public health problems in modern societies. Osteoporosis-related fractures can cause serious disability and morbidity, and can even lead to death owing to fracture-related complications. In addition, the economic burden caused by osteoporosis and fracture is expected to rise in the future. Fracture risk is determined not only by bone mineral density (BMD), but also by various risk factors associated with bone strength. In patients receiving glucocorticoid therapy, a significantly higher incidence of fractures than in controls at similar levels of BMD was documented, with an approximately twofold increase in relative risk [5]. In addition, it was estimated that the annual incidence of vertebral and non-vertebral fractures was 5.1% and 2.5%, respectively, among individuals who had initiated a glucocorticoid in the last 6 months, and 3.2% and 3.0%, respectively, among those who had used a glucocorticoid for more than 6 months [6]. More than 30% of post-menopausal women receiving chronic glucocorticoid treatment were found to have asymptomatic vertebral fractures [7]. The fracture risk assessment tool (FRAX) (https://www.sheffield.ac.uk/FRAX/index.aspx) was developed by the World

Received: 8 September 2020, **Accepted:** 11 September 2020
Corresponding author: Han Seok Choi
Division of Endocrinology and Metabolism, Department of Internal Medicine, Dongguk University Ilsan Hospital, Dongguk University College of Medicine, 27 Dongguk-ro, Ilsandong-gu, Goyang 10326, Korea
Tel: +82-31-961-5777, **Fax:** +82-31-961-7157, **E-mail:** hschoi402@dumc.or.kr

Health Organization to evaluate individuals' 10-year probability of fracture based on clinical risk factors and femoral neck BMD. Oral glucocorticoid use is also included as a risk factor in the FRAX. In this model, however, glucocorticoid use is entered as a dichotomous risk factor chosen by responding to a question asking whether the patient is currently exposed to oral glucocorticoids or has been exposed to oral glucocorticoids for more than 3 months at a prednisolone dose of 5 mg daily or more. Considering that fracture risk is largely determined by the dose and duration of glucocorticoid use, the FRAX is likely to underestimate the fracture risk among those receiving high-dose glucocorticoids. Therefore, adjustment of the FRAX-generated fracture risk according to the daily dose of glucocorticoids has been suggested [8]. To improve estimations of fracture probability, we need more accurate epidemiological data on the dose and duration of glucocorticoids and fracture risk in a large-scale population-based study.

In this issue of *Endocrinology and Metabolism*, Koh et al. [9] investigated the relationship between hip and vertebral fractures and the total amount of systemic glucocorticoid use based on data from the National Health Checkup program in Korea. The study population consisted of 1,896,159 people who participated the program in 2006 and were followed up for 2 years. All kinds of oral and parenteral glucocorticoids, including hydrocortisone, prednisolone, dexamethasone, and methylprednisolone, were included and their doses were converted to prednisolone-equivalent doses. The total amount of glucocorticoids prescribed for 6 months from the index date was calculated based on the defined daily dose (DDD). Subjects were categorized into four groups according to total glucocorticoid DDDs: non-users (DDDs=0), low users (0<DDDs≤45), intermediate users (45<DDDs≤90), and high users (90<DDDs). Hip or vertebral fracture incidence was identified from participants' claim records in the National Health Insurance Service. Vertebral fracture risk was 1.39 times higher in the low users, 1.94 times higher in the intermediate users, and 2.43 times higher in the high users than in the non-users, respectively. Hip fracture risk was 1.72 times higher in the intermediate users and 3.28 times higher in the high users than in the non-users.

Despite the higher risk of fractures among glucocorticoid users, few patients taking glucocorticoids receive BMD measurements or pharmacological treatment [10]. In this study by Koh et al. [9], fewer than 5% of glucocorticoid users received osteoporosis medication. The problem of under-treatment is associated with younger age, medical co-morbidities, and lack of BMD measurements [11]. Proactive strategies are needed to identify high-risk patients among long-term glucocorticoid users and to provide preventive management for fractures.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Han Seok Choi *https://orcid.org/0000-0002-6506-4342*

REFERENCES

1. Timmermans S, Souffriau J, Libert C. A general introduction to glucocorticoid biology. Front Immunol 2019;10:1545.
2. Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. Rheumatology (Oxford) 2011;50:1982-90.
3. Overman RA, Yeh JY, Deal CL. Prevalence of oral glucocorticoid usage in the United States: a general population perspective. Arthritis Care Res (Hoboken) 2013;65:294-8.
4. Compston J. Glucocorticoid-induced osteoporosis: an update. Endocrine 2018;61:7-16.
5. Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton III LJ, et al. A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 2004;19:893-9.
6. Amiche MA, Albaum JM, Tadrous M, Pechlivanoglou P, Levesque LE, Adachi JD, 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.
7. Angeli A, Guglielmi G, Dovio A, Capelli G, de Feo D, Giannini S, et al. High prevalence of asymptomatic vertebral fractures in post-menopausal women receiving chronic glucocorticoid therapy: a cross-sectional outpatient study. Bone 2006;39:253-9.
8. Kanis JA, Johansson H, Oden A, McCloskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int 2011;22:809-16.
9. Koh JW, Kim J, Cho H, Ha YC, Kim TY, Lee YK, et al. Effects of systemic glucocorticoid use on fracture risk: a population-based study. Endocrinol Metab 2020;35:562-70.
10. Curtis JR, Westfall AO, Allison JJ, Becker A, Casebeer L, Freeman A, et al. Longitudinal patterns in the prevention of osteoporosis in glucocorticoid-treated patients. Arthritis

Rheum 2005;52:2485-94.
11. Curtis JR, Westfall AO, Allison JJ, Freeman A, Saag KG. Channeling and adherence with alendronate and risedronate among chronic glucocorticoid users. Osteoporos Int 2006; 17:1268-74.