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Osteoporosis (A Lau, Section Editor)

Glucocorticoid-Induced Osteoporosis: Update on Management

Aprajita Jagpal, MD
Kenneth G. Saag, MD[*]

Address
[*]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham Alabama, Faculty Office Tower (FOT) Room 820D, 510 20th Street South, Birmingham, AL, 35294-3408, USA
Email: ksaag@uabmc.edu

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Abstract

Purpose of review Glucocorticoids (GCs) are potent anti-inflammatory and immunosuppressant drugs that are used to treat many inflammatory conditions across different fields of medicine. Glucocorticoid-induced osteoporosis (GIOP) is a significant comorbidity associated with long-term steroid use (> 3 months). The purpose of this review is to provide an update in the management of glucocorticoid-induced osteoporosis.
Recent findings New data for use of denosumab in GIOP includes a large clinical trial showing greater gains in bone density and no differences in adverse effects compared to risedronate. Another study suggests a reduction in hip fractures with alendronate. Meta-analyses and systematic reviews demonstrate an increase in bone mineral density as well as reduction in vertebral fractures with bisphosphonates in GIOP. Recent guidelines from the American college of Rheumatology provide concise suggestions for screening, prevention, and treatment of patients with GIOP. Adequate clinical fracture risk assessment should be obtained for each patient who is expected to receive glucocorticoids for long term. All patients should receive calcium, vitamin D supplementation, and lifestyle counselling. Pharmacologic treatment should be offered to patients who have a moderate to high risk of fractures. Oral followed by IV bisphosphonate remain the first line of treatment. The guidelines recommend other agents including teriparatide and denosumab to be considered as second- and third-line agents, respectively.
Summary Glucocorticoid-induced osteoporosis caused by long-term steroid use is associated with significant comorbidity and is often under-treated by clinicians. New clinical trials, meta-analyses, and guidelines offer new strategies for assessment and management.

Introduction

Since their introduction, glucocorticoids (GCs) have significantly improved disease outcomes and quality of life across many fields of medicine. It is estimated that 1 to 2% of populations in the UK and in the USA are receiving a GC prescription at a given time and, despite the advent of many more targeted therapeutics, the usage appears to be increasing in some populations [1, 2]. While the therapeutic benefits of GCs are great, they are obtained at the expense of adverse effects like hyperglycemia, myopathy, hypertension, adrenal insufficiency, risk of infection, and in particular, glucocorticoid-induced osteoporosis (GIOP). GCs inhibit the maturation and function of the osteoblasts inhibiting the bone formation as well stimulate osteoclasts promoting heighten bone resorption [3]. The net result of the effect of GCs on skeletal system is bone loss. Bone loss is most prominent in the areas of high content of trabecular bone while cortical bone is less affected by the GCs. GIOP is associated with an increased risk of fractures, which cause significant morbidity and mortality. Fracture risk is evident within 3 months of treatment initiation [4] and increases with daily [5] and cumulative doses [6] as well as treatment duration [7]. Some fractures such as vertebral fractures may be asymptomatic [8]. Daily doses of ≥ 15 mg prednisone or equivalent and cumulative dose of ≥ 1 g was associated with higher risk of hip fractures among glucocorticoid users in a Danish Cohort [9•]. Dosage as low as 2.5 to 7.5 mg daily of prednisone or equivalent has been reported to cause increased fracture risk [10]. Thus, there is likely no truly "safe dose" that is completely risk-free to bone.

Risk stratification

The initial step in the management of GIOP is risk stratification and identifying patients at the highest risk for fracture. Unfortunately, this practice is underutilized in many clinical practice settings and as few as 25% of patients initiating GCs receive GIOP treatment or screening [11]. Bone mineral density (BMD) was tested in only 30% among GC users with inflammatory bowel disease [12]. Several risk scores and algorithms are available for making fracture risk predictions for a patient; each has their own benefits and limitations [13, 14]. FRAX—Fracture Risk Assessment Tool score (https://www.sheffield.ac.uk/FRAX/)—is the most commonly used tool that provides 10-year probabilities of hip and major osteoporotic fractures. FRAX has several limitations in assessing fracture risk with GIOP. It makes estimation of the risk by using prednisone doses of 2.5–7.5 mg/day. Although adjustments can be made for the glucocorticoid dose [15], FRAX does not incorporate extremely high doses that patients with systemic lupus erythematous, vasculitis, or other inflammatory diseases might receive. It also does not include lower doses of steroids of < 2.5 mg of prednisone or equivalent a day which may increase the relative risk of a vertebral fracture [4]. Moreover, FRAX uses bone mineral density at the femoral neck while the effect of GCs is predominantly seen at sites richest in the trabecular bone, such as at the spine and trochanter. Additionally, the risk of a fracture in an individual patient may widely vary based on other clinical factors. Although FRAX incorporates factors like smoking, rheumatoid arthritis, and alcohol use in scoring, it does not include many other clinical risk factors such as thyroid or parathyroid disease, nutritional status, or malabsorption states, which may accompany glucocorticoid use. Thus, FRAX alone may underestimate the risk of fracture in a specific chronic disease population receiving GCs.

The American College of Rheumatology (ACR) published guidelines in 2017 for the prevention and treatment of GIOP. The guidelines advise to make a clinical fracture risk assessment as soon as possible or at least within 6 months of starting GC therapy. Further, risk stratification is based on the age of the patient (see Fig. 1). For patients under 40 years of age, no BMD testing is required unless they have a prior history of osteoporotic fracture or significant clinical factors such as weight loss, malnutrition, thyroid or parathyroid disease, smoking, alcohol use, or family history of hip fracture [16••]. All patients above age 40 years should have fracture risk assessment with FRAX score (adjusted for GC) and BMD testing. Reassessment of fracture risk is recommended every 12 months. Based on BMD, FRAX score, and history of previous fractures, a patient's fracture risk is stratified into low moderate and high-risk groups which will determine whether pharmacological intervention is indicated [16••].

Treatment of GIOP

The evidence for effectiveness of therapeutic interventions in GIOP is limited by study design and surrogate end points. The approval of drugs for GIOP is

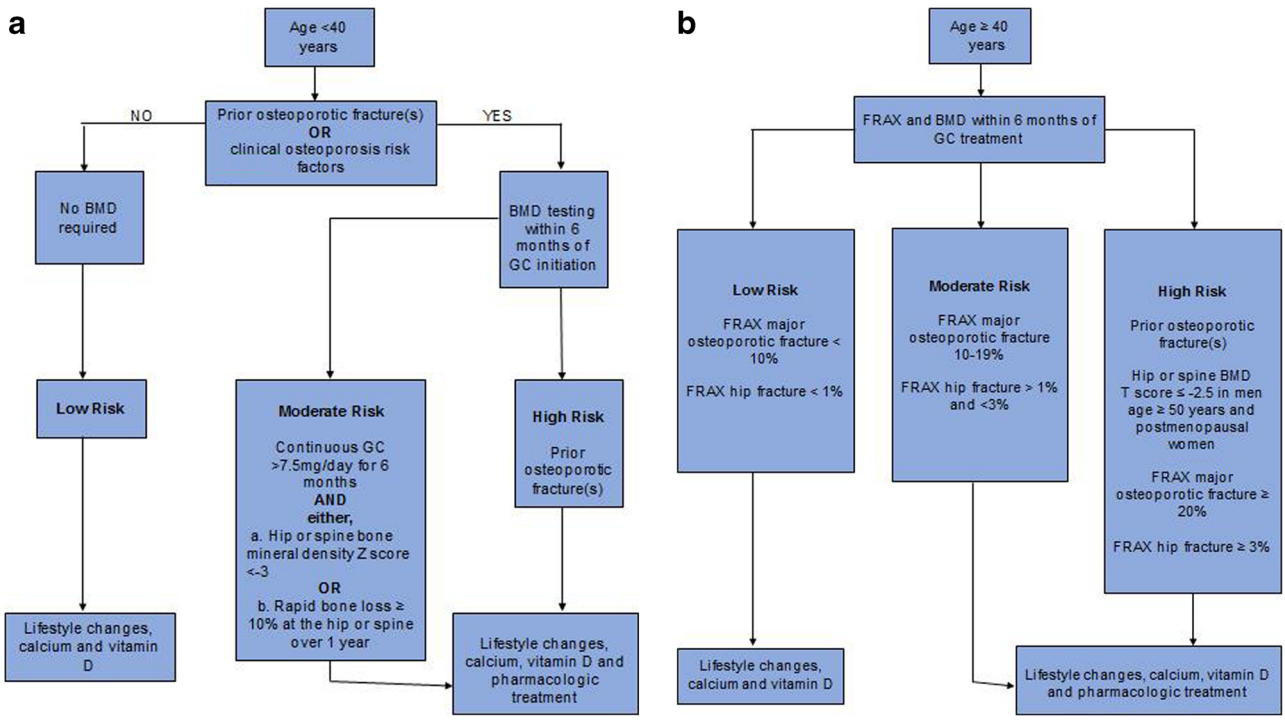

Fig. 1. a Fracture risk assessment and stratification in adult patients < 40 years of age on chronic glucocorticoids. BMD bone mineral density, GC glucocorticoids; GC treatment = prednisone > 2.5 mg/day≥ 3 months. Adapted from American College of Rheumatology 2017 guidelines on prevention and treatment of glucocorticoids induced osteoporosis with permission from John Wiley and Sons. **b** Fracture risk assessment and stratification in adult patients ≥ 40 years of age on chronic glucocorticoids. FRAX = FRAX GC adjusted and incorporates prednisone equivalent doses of 2.5–7.5 mg/day. Increase FRAX score by a relative of 15% for major osteoporotic fracture and 20% for hip fracture, if prednisone equivalent dose is > 7.5 mg/day. Adapted from American College of Rheumatology 2017 guidelines on prevention and treatment of glucocorticoid induced osteoporosis with permission from John Wiley and Sons

generally based on bone mineral density results with an extrapolation of the fracture prevention efficacy of these drugs to post-menopausal osteoporosis even though the underlying mechanisms of both conditions are very different. Due to relatively small sample sizes (related to the great difficulty in doing clinical trials in GIOP), there is a dearth of randomized controlled trial data for fracture prevention efficacy of drugs in GIOP and most of the evidence is extrapolated from observational data and meta-analyses. Additionally, the major clinical studies that evaluated efficacy of anti-osteoporotic drugs in GIOP studied BMD at spine and hip sites but not a fracture as a primary end point. Bisphosphonates, teriparatide, and denosumab are potential therapeutic options for GIOP based on available data.

Update on anti-osteoporotic medications

New observational studies and randomized controlled trials in GIOP

New observational data demonstrate the effectiveness of oral bisphosphonates in reducing fracture risk among chronic glucocorticoid users. The investigators studied patients aged 66 years and older from Ontario, Canada who initiated an oral bisphosphonate (alendronate, etidronate, or risedronate) within the first 6 months of starting chronic oral glucocorticoid therapy and matched them to patients on glucocorticoids who were unexposed to bisphosphonates. All bisphosphonates reduced the risk of vertebral fractures (alendronate ((hazard ratio [HR] 0.5, 95% confidence interval (CI) 0.4 to 0.7), etidronate (HR 0.6, 95% CI 0.5 to 0.7), and risedronate (HR 0.5 95% CI 0.4 to 0.6). Hip fracture risk also was reduced, but only by alendronate and risedronate (alendronate HR 0.5, 95% CI 0.3 to 0.8) and risedronate HR 0.6, 95% CI 0.4 to 0.9) [17•]. Another observational study showed that both alendronate and risedronate reduced vertebral and non-vertebral fractures in GIOP in the 12 month period following baseline [18]. Evidence for hip fracture reduction in GIOP with bisphosphonates is relatively limited. A promising retrospective study from Sweden examined 1802 patients aged 65 years or older who received alendronate after 3 months of prednisone therapy and compared to 1802 controls without alendronate use. Twenty-seven hip fractures were observed in the patients receiving alendronate versus 73 in patients not receiving alendronate (risk of hip fracture HR 0.4, 95% CI 0.2 to 0.6). The study was limited by its retrospective, observational design, and no data on BMD was available [19•]. Presently, alendronate, risedronate, and zoledronic acid are currently approved by the Food and Drug Administration (FDA) for treatment of GIOP. A recent randomized controlled trial has indicated that ibandronate may be effective in GIOP as well, although long-term studies are needed to explicitly study its effect [20•]. This study from Korea randomized 167 women, who had taken > 5 mg of prednisone for 3 or more months and had a lumbar spine (L1–L4) *T* score of < – 1.0 and ≥ – 2.5, to receive ibandronate every 4 weeks or placebo. Treatment with ibandronate was associated with an increase in BMD at L spine at 48 weeks compared to placebo (BMD percent change + 3.7 vs – 1.9% respectively; $p < 0.0001$). No fractures were observed in either group. These results need validation in larger international cohorts.

Teriparatide, a recombinant DNA origin human parathyroid hormone, stimulates osteoblast activity and thus may counteract a key underlying mechanism of GIOP. Compared to alendronate, greater increases in BMD at lumbar

spine and femoral neck with reduction in vertebral fractures were seen with teriparatide in a randomized controlled trial [21]. In a second study, similar benefits of increased BMD at spine and hip from teriparatide were seen in comparison to risedronate at 18 months, though the participants in this particular study were only men. A decrease trend in fractures was observed but the study was underpowered to demonstrate a significant difference [22]. Not only did teriparatide increase BMD, but it also impacted the qualitative microarchitecture of the bone as measured by trabecular bone score in GIOP [23•].

Denosumab, a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, is effective in post-menopausal osteoporosis [24], but data for its use in GIOP until recently has been limited. A few small prospective studies have demonstrated its benefit in GIOP, but larger trials are needed to confirm the findings. A prospective study of 29 patients receiving GCs received denosumab 60 mg at baseline and 6 months. BMD and bone turn over markers were measured (N-terminal cross-linked telopeptide of type I collagen (NTX) and bone-specific alkaline phosphatase (BAP) levels). Denosumab treatment reduced the bone marker levels and improved BMD at lumbar spine and femoral neck at 12 months [25]. The study was small, and the lack of a control group was a major limiting factor. Another prospective study of 36 patients who were receiving GCs for their pulmonary disease demonstrated an increase in BMD at lumbar spine by 3.2% after treatment with denosumab at 12 months [26]. A clinical trial from Hong Kong randomized 42 women, who were receiving long-term prednisolone 2.5 mg a day or more for more than a year and were also being treated with oral bisphosphonate for 2 or more years, to either switch to denosumab or continue bisphosphonate [27]. At the end of 12 months, a higher increase in BMD at spine was seen in the patients who switched to denosumab compared to those who continued oral bisphosphonate. However, a study from Japan showed conflicting results where denosumab increased BMD at spine and hip at 12 months but more so in patients on glucocorticoids who were not previously treated with bisphosphonates compared to those who were pretreated with bisphosphonates. The reasons for this discrepancy were not clear; however, the study was limited by small sample size ($n = 48$), a retrospective design, and short follow-up [28]. Until 2018, studies have had small sample sizes and many other limitations, but they have been provocative in suggesting a potential role of denosumab in GIOP management. Recently, a 24-month, double-blind, double dummy randomized clinical trial of denosumab enrolled adults at 79 international centers who were receiving glucocorticoids (≥ 7.5 mg prednisone daily or equivalent) [29••]. Patients were randomized to receive denosumab with oral placebo or risedronate with subcutaneous placebo for 24 months. Compared to risedronate, denosumab was non-inferior in terms of percentage increases in bone mineral density at the lumbar spine among glucocorticoid users at 12 months. It was also superior to risedronate in increasing bone mineral density at lumbar spine, total hip, and femoral neck at 12 months (secondary end points). Adverse effects and fractures were reported similarly in both groups. This study provided promising data suggesting that denosumab could be a potential therapeutic option for patients with GIOP.

Timing of initiation of anti-osteoporotic medication may also impact the efficacy in reducing the fracture risk. A 48% reduction at 1 year and 32% at

3 years in osteoporotic fractures was noted in an observational study of women aged 50 years or above on chronic glucocorticoids who initiated anti-osteoporotic medication within 90 days of steroid use [30]. Thus, early initiation of therapy with ongoing glucocorticoid therapy may be more efficacious.

Meta-analysis and systematic reviews

A meta-analysis by Kan et al. included a total of 9 studies with 1134 patients with rheumatic diseases on alendronate. While it did not find a significant reduction in vertebral or non-vertebral fractures, an increase in BMD was noted at the lumbar spine (mean difference = 3.7, 95% CI 2.6 to 4.7, $P < 0.05$), total hip (mean difference = 2.1, 95% CI 0.4 to 3.7, $P < 0.05$), and trochanter (mean difference = 1.7, 95% CI 0.8 to 2.6, $P < 0.05$) [31•]. It is possible that due to short follow-up periods, studies included in the analysis were underpowered to detect a difference; however, a prior published systematic review and meta-analysis reported reduction in vertebral fractures with bisphosphonates [32]. A more recent (2016) Cochrane review analyzed 27 randomized controlled trials of prevention or treatment of GIOP with 3075 participants [33•]. Patients included were adults taking a mean daily GC dose of 5 mg or more and receiving active treatment with bisphosphonate of any type [33•]. Pooled analysis for incident vertebral fractures revealed that treatment with bisphosphonates reduced vertebral fractures by 40% with a number needed to treat of 31. Non-vertebral fractures were numerically reduced as well, but differences were not statistically different. The study also suggested an increase in BMD at lumbar spine and femoral neck with bisphosphonate treatment.

Another meta-analysis compared the efficacy of teriparatide to bisphosphonates in osteoporosis [34•]. It included 1967 patients with osteoporosis from 8 randomized controlled studies with drug interventions, and subgroup analysis was performed according the cause of osteoporosis. Among patients with GIOP, higher increases in BMD at lumbar spine, total hip, and femoral neck were noted with teriparatide compared to bisphosphonates. These patients also had lower risk of vertebral fractures; however, no difference was noted in non-vertebral fractures in comparison to bisphosphonates.

New ACR GIOP treatment recommendations

Different guidelines in the past have proposed different thresholds for pharmacologic interventions. The American College of Rheumatology published updated guidelines in 2017 on prevention and treatment of GIOP and recommend anti-osteoporotic medication treatment for patients in moderate and high fracture risk groups (see "Risk stratification" above; Fig. 1). The ACR guideline group recommended that all patients on long-term GC therapy should receive calcium and vitamin D supplementation along with counselling on lifestyle measures such as nutritious diet, smoking cessation, and regular exercise. Oral bisphosphonates were recommended as the first-line treatment, though intravenous bisphosphonate could be used, after considering factors such as medication compliance, cost, and patient preference. Even though teriparatide is likely superior to bisphosphonates with respect to bone density and vertebral fracture outcomes, the current ACR guidelines recommend bisphosphonates over teriparatide for GIOP. High-cost burden and

inconvenience associated with daily injections are significant limitations and influenced this recommendation. Denosumab was suggested after giving due consideration to bisphosphonates and teriparatide. These guidelines represent an update and a general advance over the more complex earlier guideline from the ACR [35]. Like all guidelines, they are not perfect and some critiques have followed such as the absence of discussion defining select circumstances where high-risk patients might be considered for one of the later tier drugs, such as teriparatide, sooner rather than later [36].

Conclusion

Glucocorticoid-induced osteoporosis is markedly under recognized and undertreated [37, 38•]. Increased awareness among providers of different specialties who manage patients with long-term glucocorticoid use is needed to risk stratify and start pharmacologic treatment in those at high risk of fracture. Recent ACR guidelines provide updated evidence-based clinical practice recommendations which if implemented could significantly improve outcomes among GC users. While new agents may evolve as treatment options in near future, evidence only supports efficacy for bisphosphonates, teriparatide, and denosumab.

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Compliance with Ethical Standards

Conflict of Interest
Aprajita Jagpal declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human participants or animals performed by any of the authors.

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