



Glucocorticoid-induced osteoporosis

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Therapeutic use of glucocorticoids can lead to many well-known adverse events [1]. Of all potential serious side effects, glucocorticoid-induced osteoporosis (GIOP) is one of the most devastating complications of protracted glucocorticoid therapy in rheumatoid arthritis (RA) [2,3]. GIOP is second in frequency only to the osteoporosis that occurs after menopause and is the most common form of drug-induced osteoporosis. Lukert and Raisz have estimated that over 50% of chronic glucocorticoid users will develop bone loss leading to fracture [4]. Although much has been written about the association of glucocorticoids with bone disease among patients with chronic inflammatory conditions, many issues remain unsettled. This article focuses on areas of continued controversies, including the epidemiology and pathogenesis of GIOP, specification of a “safe” dose, methods for diagnosis of GIOP, and an evidence-based approach for GIOP prevention.

Epidemiology

Community surveys indicate that glucocorticoids are used by an estimated 0.2% to 0.5% of the general population [5–7]. Patients with RA, chronic obstructive pulmonary disease (COPD), asthma, and inflammatory bowel disease and transplant recipients comprise the majority of chronic glucocorticoid users internationally [6,7].

During the first 6 to 12 months of glucocorticoid therapy, there is an initial rapid loss of 3% to 27% of bone mineral density (BMD) [8–12]. Trabecular bone is preferentially affected, followed by losses in cortical bone [13]. The literature is divided, however, on whether trabecular bone is lost most rapidly from the trochanter [14–18] or the lumbar spine [19,20]. Bone

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loss may be potentially reversible by lowering or cessation of the glucocorticoid [8]. After approximately 2 years of glucocorticoid therapy, there is a slowed rate of bone loss in many patients. However, BMD continues to be lost at a rate higher than with normal aging [4,21].

In addition to older women on glucocorticoids, significant bone loss leading to fractures may occur in men [20,22–24], pre-menopausal women [25], and even in children [26] (Fig. 1). However, people who already have very low bone mass (such as postmenopausal women who have not taken

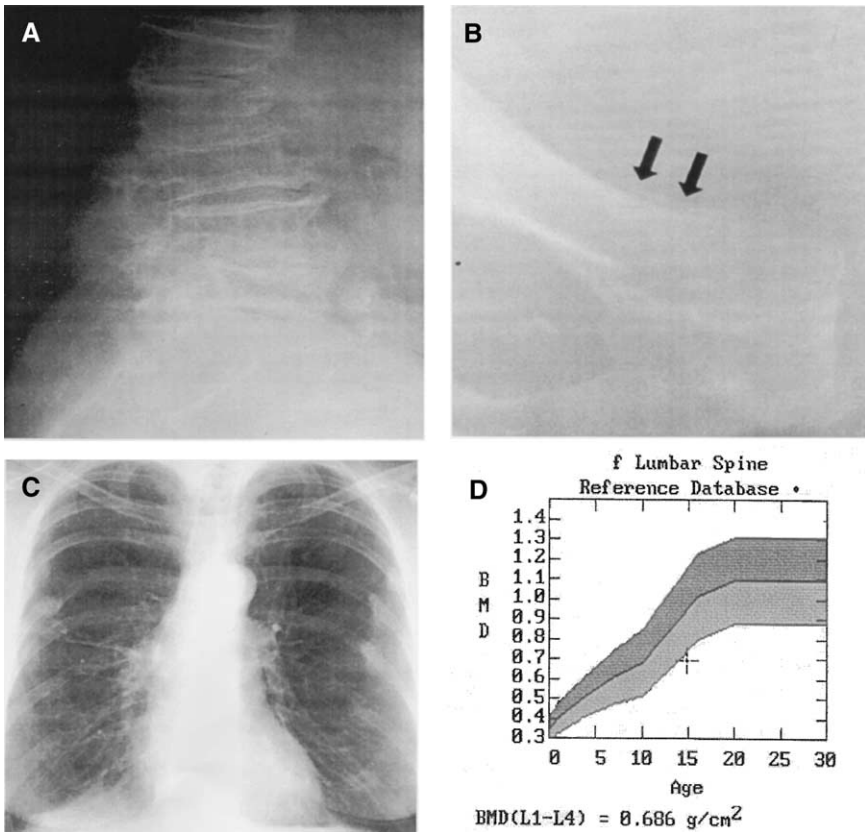


Fig. 1. Glucocorticoid-induced osteoporosis. (A) Multiple vertebral compression fractures in a 75-year-old white man with severe COPD treated with over 10 years of prednisone at an average dose of 20 mg/d. (B) Pelvic insufficiency fracture (*arrows* show periosteal elevation) in a 43-year-old perimenopausal Caucasian woman with systemic lupus erythematosus who has undergone a recent renal transplant for lupus nephritis. The patient had already experienced a lumbar vertebral compression fracture. (C) Healing rib fractures in a 57-year-old African American woman with severe bronchiectasis treated with chronic glucocorticoids. (D) Low lumbar spine BMD in a 15-year-old Caucasian boy with cystic fibrosis requiring intermittent glucocorticoids for recurrent sinusitis. Bone mass remained more than 2 standard deviations below norms even after adjustment to actual bone age.

hormone replacement therapy) are more likely to reach a fracture threshold sooner. Certain diseases and treatments concomitantly accelerate bone loss. RA patients on glucocorticoids have generally been found to have lower BMD than their non-user counterparts [27,28]. Independent of glucocorticoids, RA causes regional and generalized bone loss [14,16,29–33], and RA patients are at higher risk for fracture [28,34,35]. A large amount of literature confirms the negative effects of glucocorticoids on bone in other inflammatory diseases very commonly requiring glucocorticoids [6] such as asthma [36–39], COPD [22,40], inflammatory bowel disease [41–44], nephrotic syndrome [45], polymyalgia rheumatica [46], sarcoidosis [47], systemic lupus erythematosus [48–50], and organ transplantation [51–55].

There is controversy over whether a safe glucocorticoid dose exists, particularly in the context of RA treatments [56]. A number of cross-sectional and even some longitudinal investigations have failed to identify an adverse effect of low-dose glucocorticoids on bone in RA patients [18,30,31,57–59]. Some authors have proposed that glucocorticoids do not adversely affect bone and may even protect bone in RA patients by improving functional status and reducing circulating pro-inflammatory cytokines that are deleterious to bone [30,59]. Observational studies have suggested that prednisone doses below 5 mg/d may have fewer negative effects on bone among RA patients [1,19]. However, several of these studies were small, and the possibility of missing an important effect due to a Type II statistical error exists. A meta-analysis concluded that the effect of glucocorticoids on bones among RA patients was at worst modest [60]. However, one of the included studies reported improved BMD at the lumbar spine but paradoxically showed bone loss at all other locations measured [17]. When the authors pooled only randomized controlled trials ($n = 2$), they observed a deleterious effect of glucocorticoids on bone. Strengthening the argument against a “safe” glucocorticoid threshold, a single oral dose of only 2.5-mg of prednisone has almost immediate effects on serum osteocalcin levels, which is a measure of bone formation [61]. Even nonsystemically administered glucocorticoids may have biologic effects on bone [62–64]. Even though inhaled glucocorticoids are associated with an up to 1 standard deviation decline in BMD t scores when used chronically [65,66], they are preferred over oral glucocorticoids for patients with serious pulmonary disorders [67].

Because glucocorticoids may affect bone quantity *and* quality [68], fractures are the outcome measure of greatest importance. Some studies suggest that glucocorticoid-treated patients may experience fractures at a higher BMD threshold than nonusers [69]. However, three more recent studies refute the premise of a higher BMD fracture threshold among glucocorticoid-treated patients [70–72]. Studies of steroid dose effects are confounded by the variable timing of glucocorticoid administration, differing disease process, variable alternative osteoporosis risk factors (independent of glucocorticoid use), and the fact that fracture risk is

ultimately determined by factors other than BMD. Case-control studies of general populations show that glucocorticoids lead to a roughly twofold increased risk of fractures independent of age, gender, and the presence of RA [34,73].

Among RA patients, who constitute the largest group of glucocorticoid users overall, an increased rate of fractures has been observed in cross-sectional and longitudinal studies [1,12,74–76]. A large observational study of RA patients indicated that a woman taking an average dosage of 8.6 mg of prednisone had a nearly 33% chance of a self-reported clinical fracture after 5 years of follow-up [76]. Other observational studies suggest that over 40% of long-term users will ultimately fracture [13,77]. At least two retrospective studies identify fractures as one of the most commonly documented complications of supraphysiologic glucocorticoid use [1,75]. However, observational studies of this type may be prone to selection bias and confounding by indication, whereby patients with more severe and active inflammatory disease (who are more commonly treated with glucocorticoids) are also more likely to have an adverse outcome independent of glucocorticoid use. Placebo arms of randomized controlled trials (RCTs) document about a 15% incidence of morphometrically defined vertebral fractures after 1 year in patients on median doses of less than 10 mg/d [78,79]. In the only RCT of prednisone versus placebo in RA, five patients on low-dose prednisone (12.5%) and two patients on placebo (4.9%) developed new vertebral fractures within 2 years [80]. The full adverse effects of glucocorticoids may be underestimated because only T2 through L5 were quantitated in this study. Data from additional clinical trials include the control arms of large Phase III studies of alendronate and risedronate for GIOP prevention and treatment [78,79,81]. In these large clinical trials, only postmenopausal women and a few men, but not premenopausal women, experienced fractures. RCTs have limitations because inherent selection bias of patients enrolled in these studies and the lack of long-term follow-up fail to clarify the full magnitude of the fracture risk among community-dwelling patients who often take glucocorticoids for many years.

Debate continues on whether peak or cumulative dose is most strongly associated with bone loss. Although alternate-day therapy may afford modest benefits for bone preservation over daily therapy [82], the cumulative glucocorticoid seems more important than peak dose based on a number of studies [13–15,83]. In contrast to these data, a secondary analysis of the large United Kingdom General Practice Research Database (GPRD) found that adverse effects of glucocorticoids on bone occurred rapidly and were most strongly related to daily over cumulative dose [84]. In this study, a monotonic relationship was identified between clinical fractures and glucocorticoid dose up to about 20 mg/d and increased in a more exponential fashion thereafter (Fig. 2). Most glucocorticoid users in GPRD did not have inflammatory diseases requiring chronic doses of glucocorti-

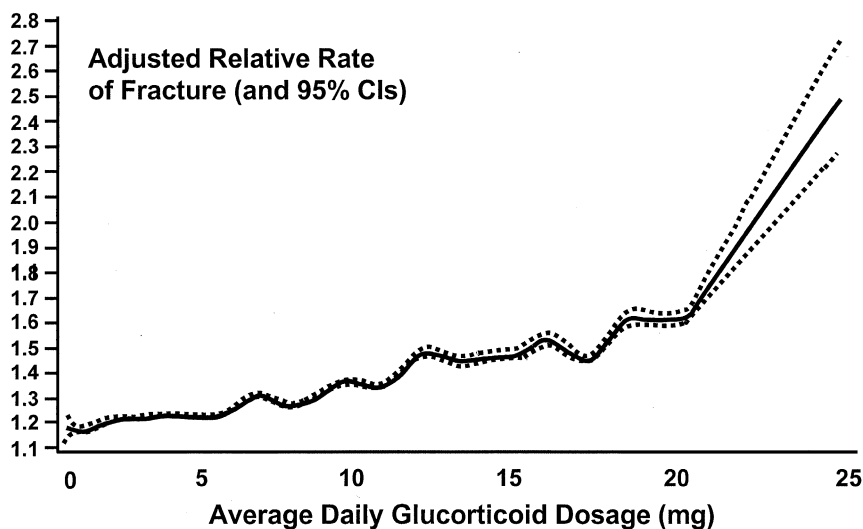


Fig. 2. Effects of daily prednisolone dose on nonvertebral fractures. Dashed lines represent 95% CI. (Adapted from van Staa TP, Leukens HGM, Abenham L, et al. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatology (Oxford)* 2000;39:1383–9; with permission.)

coids, as evidenced by a median glucocorticoid duration of approximately 30 days [85]. The presence of fractures with even low-dose oral therapy [85] further argues against a “safe” glucocorticoid dose from the standpoint of bone.

Pathogenesis

The etiology of GIOP is multi-factorial and occurs, in many cases, concomitantly with normal age and menopause-associated bone loss. There are two major pathways by which glucocorticoids lead to abnormalities in bone metabolism: (i) a reduction in bone formation and (ii) an increase in bone resorption [86–88]. Although the pathogenesis of GIOP is somewhat unsettled, a direct inhibition on osteoblast activity by glucocorticoids is the most favored principal mechanism [89,90]. Histologically, this is indicated by reduced trabecular wall thickness [91,92]. Glucocorticoids cause a decrease in absolute number of osteoblasts and their premature death by apoptosis [93] (Fig. 3). Glucocorticoids modulate osteoblasts’ response to skeletal growth factors such as IGF-1, IGF-2, IGF-binding proteins, and cytokines (eg, TGF- β and platelet-derived growth factor- β) [87]. Osteoblast inhibition is evident by decreases in serum osteocalcin levels [62,94,95]. Osteoblast dysfunction results in incomplete repair of the bone remodeling lacunae [90].

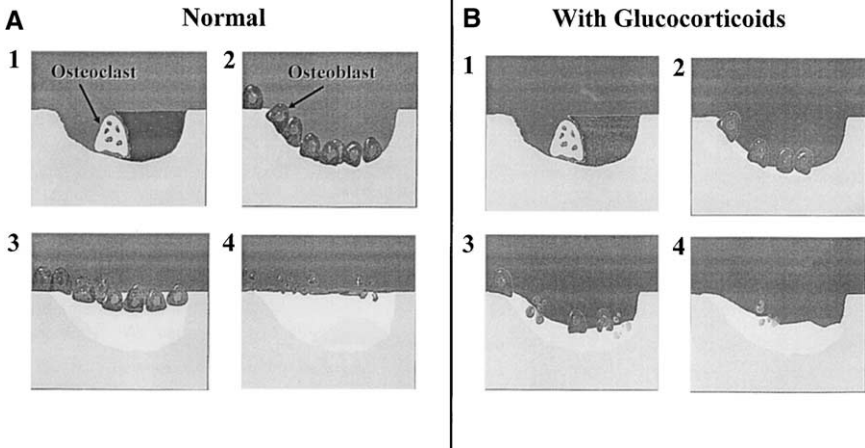


Fig. 3. Normal sequential cycle of bone remodeling shown (A) with an abnormal one caused by glucocorticoid excess (B). Glucocorticoid-associated osteoporosis is caused by a decrease in absolute number of osteoblasts and their premature death by apoptosis. Osteoblast dysfunction results in the incomplete repair of bone remodeling lacunae. (Adapted from Manolagas SC, Weinstein RS. New developments in the pathogenesis and treatment of steroid-induced osteoporosis. *J Bone Miner Res* 1999;14:1061–6; with permission.)

Enhanced osteoclast-mediated bone resorption is the other mechanistic pathway to GIOP. There are only limited data, however, to show that glucocorticoids significantly inhibit calcium absorption through the gastrointestinal tract [96,97], increased renal calcium loss [98,99], or diminished sex hormone production [100–102], all of which could lead to increased bone resorption. Effects on calcium may be mediated partially by direct effects of glucocorticoids on vitamin D or its receptors [94]. As reported by some, but not by all, investigators, reduced serum levels of ionized calcium may lead to a relative secondary hyperparathyroidism and increased bone resorption [99]. As another even more compelling mechanism of bone resorption, glucocorticoids suppress osteoprotegerin (OPG) and concurrently stimulate OPG ligand production by osteoblastic lineage cells [103,104].

Diagnostic evaluation of the patient on glucocorticoids

There should be a high suspicion for potential bone loss among all patients initiating or chronically using glucocorticoids. The most accurate way to determine a glucocorticoid user's osteoporosis status is to assess bone mass, typically using dual-energy x-ray absorptiometry (DXA). Despite the precision of this approach and the vast benefits of DXA, the use of different DXA devices and disparities between the sites of measurement limit this technique [105]. If only a single site can be measured in an older patient on glucocorticoids, a hip DXA is preferred.

Recommendations for bone mass measurement of patients on glucocorticoids have been proposed by different medical societies and ad hoc panels and are reimbursed under the US Bone Mass Measurement Act and [106–110]. Most guidelines suggest a BMD test if the patient will receive treatment with greater than physiologic glucocorticoid usage (≥ 7.5 mg of prednisone or its equivalent per day) and treatment for at least 1 to 6 months. The lumbar spine and trochanter demonstrate rapid bone loss with glucocorticoids and respond reliably to effective GIOP interventions and thus are sensitive imaging sites. Poor precision and localized effects of arthritis may limit the use of peripheral BMD measurements in the wrist, fingers, and heels. Quantitative computerized tomography (QCT) can also be used but may overestimate the effects of glucocorticoid on bone because glucocorticoids increase bone marrow fat.

It is also important to consider gonadal status in chronic glucocorticoid users. In perimenopausal women, measurement of a FSH and estradiol level may provide further clarification. Pre-menopausal women with chronic inflammatory disorders also may be estrogen deficient, often manifested by oligo- or amenorrhea. Measurement of free testosterone is warranted in men on chronic glucocorticoids or those with symptoms of gonadal insufficiency.

Although a decline in BMD strongly correlates with fracture risk and BMD is the best measurable predictor currently known, the rate of bone turnover, bone quality, and other factors play important independent roles in fracture risk [68]. A very high value of a bone resorption marker (such as urinary N-telopeptides or deoxypyridinoline cross links) may identify patients with particularly rapid bone turnover or substantiate a lack of response to anti-resorptive agents. An elevated 24-hour urinary calcium-to-creatinine ratio (greater than 250 mg for women or 300 mg for men) is also indicative of rapid bone turnover, such as seen among patients newly using glucocorticoid.

Even among patients who are assumed to have osteoporosis on the basis of chronic glucocorticoid use, postmenopausal status, their severe inflammatory condition, selective screening for other causes of bone loss should be considered. Hyperparathyroidism, hyperthyroidism, osteomalacia (due to poor dietary vitamin D intake and inadequate sun exposure), or multiple myeloma can all mimic or contribute to low bone mass among patients on glucocorticoids. In particular, a 25-OH vitamin D measurement is helpful in identifying patients with low or low normal vitamin D stores who might benefit from supplementation. Although not indicated in all glucocorticoid users with low BMD, laboratory evaluation for these and other conditions should be undertaken based on clinical suspicion.

Prevention and treatment

Based on this accumulating data showing an increased risk for bone loss among RA patients (particularly patients on steroids), there is a need to

identify effective strategies aimed at mitigating possible toxicity. The American College of Rheumatology and other specialty groups have released recommendations for the prevention and treatment of GIOP [107,108,111,112]. These recommendations advocate an increasingly aggressive approach to this serious problem based on accumulating literature demonstrating good efficacy of several anti-osteoporosis compounds, particularly the amino-bisphosphonates.

The most effective intervention for the prevention of bone loss and fractures among glucocorticoid users is glucocorticoid discontinuation or, at a minimum, dose reduction [113]. This is not always possible because of the severity of many chronic inflammatory diseases. Putative bone-sparing glucocorticoids, such as deflazacort, have been identified [17,114] but are not available in the United States and may not be safer than conventional glucocorticoids at an equipotent dose. A number of the therapeutic agents used in postmenopausal osteoporosis have particular relevance for GIOP. Vitamin D and calcium may increase gastrointestinal calcium intake and limit renal losses, thiazide diuretics may decrease urinary calcium excretion, estrogen and testosterone supplements may help offset gonadal deficiency, bisphosphonates and calcitonin may prevent bone resorption, and fluoride and parathyroid hormone (PTH) might stimulate osteoblastic bone formation.

Calcium and vitamin D

Calcium decreases bone resorption as measured by urinary hydroxyproline [115]. However, calcium alone may not prevent bone loss, particularly in patients prone to poor absorption [116]. Elemental calcium at 1200 to 1500 mg/d is necessary, although it is generally not sufficient as a sole therapy for most patients on glucocorticoids.

Vitamin D can be administered in a variety of formulations that have been investigated for GIOP prevention and treatment [13,117–119]. In a prevention study, calcium, calcitriol, and calcitonin used in varying combinations were given to patients for 1 year. Patients were followed for an additional second year off therapy. At the lumbar spine, subjects randomized to receive a combination containing calcitriol experienced significantly less bone loss than those receiving calcium alone. In Year 2, a slight lumbar spine BMD increase was seen among subjects who received calcitonin. No differential effects between the three treatment arms were observed at the femoral neck, where bone loss occurred in all three treatment groups [119]. Indicative of the need to carefully monitor serum and urinary calcium in patients receiving 0.5 to 1.0 μg of calcitriol (when used in combination with calcium), nearly 25% of patients receiving calcitriol developed hypercalcemia. Other studies of active D metabolites, particularly alphacalcidol, have shown efficacy in several [117,118] but not all studies [13].

Inactivated vitamin D preparations may also have merit in GIOP. In a 2-year trial of RA patients on chronic low doses of glucocorticoids, 1000 mg of calcium carbonate and 500 IU of vitamin D prevented bone loss in the lumbar spine and trochanter [120]. An earlier study of smaller doses of vitamin D and calcium did not demonstrate a significant differential effect of from calcium alone, although a small increase in BMD was noted in both groups [121]. Data are more equivocal with respect to ergocalciferol, typically administered orally as 50,000 units once weekly [122]. A meta-analysis of different formulations of vitamin D, including its active metabolites and analogues, demonstrated a moderate pooled effect size at the lumbar spine of 0.6 (95% confidence intervals 0.34–0.85) [123]. The meta-analysis conclusions did not vary if only active vitamin D metabolites were analyzed or if the analysis was restricted only to prevention studies. A Cochrane review of this literature has also concluded that vitamin D is of benefit to chronic glucocorticoid users [124]. Due to the impairment in calcium absorption mediated by glucocorticoids and the common occurrence of vitamin D deficiency among housebound patients suffering with chronic inflammatory conditions, vitamin D should be supplemented in all glucocorticoid users [107,124]. This can be simply and efficaciously accomplished by providing 800 IU/d of vitamin D3, available through a multivitamin and the additional D contained in many calcium supplements. Provided that there is careful use of exogenous calcium and monitoring of urine and serum calcium, vitamin D might alternatively be administered as calcitriol.

Thiazide diuretics

Only one study has specifically examined the efficacy of thiazides agents in glucocorticoid-treated patients. In combination with dietary sodium restriction, hydrochlorothiazide 50 mg twice a day improved total body calcium economy [125]. Despite this paucity of evidence, thiazides may make pathophysiologic sense during the early phase of glucocorticoid use when there is profound hypercalciuria. On the other hand, there are substantial side effects of thiazides.

Calcitonin

When bone mass is measured at the lumbar spine, calcitonin is weakly effective at preventing and treating GIOP. Similar to the Sambrook prevention trial [119], Adachi et al found that spinal bone density declined on placebo (5%), whereas the calcitonin-treated group had a nonsignificant decline of 1.3% over 1 year [126]. Although less lumbar bone was lost in an observational study of sarcoid patients who received calcitonin for GIOP prevention [127], a randomized controlled prevention study in polymyalgia rheumatica patients did not show greater bone preservation with injectable

calcitonin [128]. In one of three treatment studies, placebo patients lost 7.8% BMD over 2 years, whereas the nasal calcitonin-treated group had an increase of 2.8% [129]. An asthma treatment study of subcutaneous calcitonin showed similar levels of BMD gain in the forearm [130]. However, at a lower dose (100 IU/d), nasal calcitonin was not efficacious in treating the spine [131]. For GIOP, calcitonin is a relatively weak antiresorptive agent. It potentially maintains bone mass, but in most studies calcitonin does not lead to a marked increase in BMD. There has not been a documented benefit of its effects on fracture reduction in GIOP.

Estrogen and testosterone

In the only randomized controlled trial of estrogen replacement therapy (ERT) in GIOP, postmenopausal women with rheumatoid arthritis received ERT (transdermal estradiol 50 µg/d) or calcium supplementation (400 IU/d) [132]. At the end of 2 years, women on ERT had higher bone density in the spine than those receiving calcium alone. There were no significant differences at the femur. Two small observational studies of ERT demonstrated reduced bone loss in the spine among chronic glucocorticoid users [133,134].

A randomized crossover trial of testosterone in the treatment of GIOP examined men with asthma [135]. All hypogonadal men were also given calcium supplements (1000 mg/d). The results of this study indicate that BMD of the lumbar spine increased significantly on testosterone, whereas it decreased with placebo. In men with low serum testosterone, intermittent administration of medroxyprogesterone may help maintain bone mass [136]. No primary prevention studies of estrogen have been completed, and fracture data are similarly unavailable. Thus, although the data are rather sparse, hormone replacement therapy may be justified in postmenopausal, premenopausal women who are oligomenorrheic or amenorrheic (often on the basis of their chronic inflammatory diseases) and in men with hypogonadism. Selective estrogen receptor modulators (SERMs) may offer an as yet unproven therapeutic option in GIOP.

Bisphosphonates

When administered over 1 or 2 years to patients on glucocorticoids for a variety of chronic inflammatory disorders, etidronate, pamidronate, alendronate, and risedronate are efficacious in preventing or treating bone loss at the spine and in regions of the hip. A number of observational or open-label studies [137–144] and at least seven randomized controlled clinical trials [122,144–149] have examined the effects of etidronate on GIOP. Of the randomized studies, most demonstrated increased [122,145,147] or preserved lumbar BMD [144,148] compared with placebo, which often included calcium. A meta-analysis has confirmed the perceived

BMD benefits of this therapy in GIOP [150]. In the largest prevention trial, cyclical etidronate was instituted within 100 days of prednisone initiation in 141 men and women, beginning prednisone therapy for a variety of conditions [122]. The placebo group had a decrease in lumbar BMD of 3.2%, whereas the treatment group had an increase of 0.6% at 1 year. Similar effects were seen at the trochanter. Bone density at the femoral neck did not differ significantly between groups. A trend toward a significant fracture reduction was seen in the postmenopausal women in this study. The largest treatment study with etidronate also confirmed that etidronate, when administered with calcium and vitamin D, resulted in a significant 4.5% increase in lumbar BMD [147].

Alendronate has proven efficacy in preventing and treating bone loss associated with glucocorticoid use and in preventing vertebral fractures [79,151,152]. In the combined report from two multinational studies, 477 new and chronic glucocorticoid users were studied, including postmenopausal women, premenopausal women, and men. At the spine, there was a significant increase in BMD of 2.9% on 10 mg of alendronate and a loss of 0.4% on placebo. Similar effects were seen at the trochanter, and smaller but significant gains in BMD were noted at the femoral neck [79]. A second-year extension to this study among 208 (37%) of the original subjects who continued to take ≥ 7.5 mg of prednisone (or equivalent glucocorticoid) documented similar beneficial effects at the spine, trochanter, and femoral neck [153]. A significant 90% reduction in an overall small number of incident vertebral fractures was observed. Alendronate (5 mg) was statistically equivalent to 10 mg except among postmenopausal women not receiving estrogen, where 10 mg resulted in significantly greater increases in lumbar BMD.

Risedronate at 2.5 and 5.0 mg/d maintained or increased bone mass at the lumbar spine, trochanter, and femoral neck in patients beginning glucocorticoids [78]. At the lumbar spine, bone mass was maintained with an increase of 0.6% in the group receiving 5 mg of risedronate compared with a loss of 2.8% in the control group. Similar effects were seen at the trochanter. At the femoral neck, bone mass increased 0.8% in those given 5 mg of risedronate with a loss of 3.1% in the control group. In patients already on long-term glucocorticoids, 2.5 and 5.0 mg of risedronate maintained or increased bone mass at the lumbar spine, trochanter, and femoral neck [81]. Pooled data from the two risedronate studies demonstrated a 58% to 70% reduction in vertebral fracture rate [154].

Intravenous pamidronate may afford another effective therapeutic alternative for highly selected individuals who are not candidates for oral bisphosphonate therapy [155–159]. As measured by QCT (a technique that may over estimate of trabecular bone mass change), a >19% increase in lumbar BMD at 1 year was seen in a randomized controlled study [158].

In all large randomized controlled trials of bisphosphonates [155,157–159], bone mass was maintained or increased with bisphosphonate therapy,

whereas a decline was generally seen in the control group of the prevention studies. In the treatment studies, a bisphosphonate was always more effective than control therapy, although the control groups did not always lose bone at a significant rate. A Cochrane review further concluded that bisphosphonates are effective in preventing and treating glucocorticoid-associated bone loss at the lumbar spine and the femoral neck [124]. The BMD and fracture data from large RCTs of alendronate and risedronate are shown in Table 1. These studies were not head-to-head, and differing patient populations and outcome definitions limit comparability.

Table 1

Large, randomized, controlled clinical trials evaluating alendronate and risedronate for the prevention or treatment of GIOP

Agent/ indication (no. of points)	Glucocorticoid (dose/d) ^a	Bisphosphonate (dose/d) ^b	Mean (\pm SD) change in lumbar spine BMD from baseline (%)	Relative reduction in vertebral fracture risk ^c (% reduction vs placebo)
Alendronate/ prevention and treatment (<i>n</i> = 477) [79]	10 mg (median)	5 mg	2.1 \pm 0.3	38% (<i>P</i> > 0.05) (combined data from both groups)
	5–135 mg (range)	10 mg	2.9 \pm 0.3	
		Placebo	-0.04 \pm 0.3	
Alendronate/ prevention and treatment (extension) (<i>n</i> = 208) [153]	17–21 mg (mean)	2.5/10 mg	3.7 \pm 0.57	90% (<i>P</i> = 0.03) (combined data from all groups)
		5 mg	2.8 \pm 0.62	
		10 mg	3.8 \pm 0.68	
		Placebo	-0.8 \pm 0.64	
Risedronate/ prevention (<i>n</i> = 224) [78]	20–22 mg (mean)	2.5 mg	-0.1 \pm 0.7	71% (<i>P</i> = 0.07)
		5 mg	0.6 \pm 0.5	
		Placebo	-2.8 \pm 0.5	
Risedronate/ treatment (<i>n</i> = 290) [81]	15 mg (mean)	2.5 mg	1.9 \pm 0.5	70% (<i>P</i> = 0.12) (combined data from both groups)
		5 mg	2.9 \pm 0.5	
		Placebo	0.4 \pm 0.4	
Risedronate/ pooled results from prevention/ treatment studies (<i>n</i> = 518) [154]	17–18 mg	2.5 mg	1.3 \pm 0.41	58% (<i>P</i> = 0.08) 70% (<i>P</i> = 0.01)
		5 mg	1.9 \pm 0.38	
		Placebo	-1.0 \pm 0.35	

Abbreviations: BMD, bone mineral density; GIOP, glucocorticoid-induced osteoporosis; SD, standard deviation.

^a Glucocorticoid dose is reported as mg/d of prednisone or its equivalent.

^b Patients received calcium and vitamin D supplementation in four trials [25,77,153,169] and calcium alone in one trial [126].

^c Percentages are reported for the number of evaluable patients, which varied according to the study.

Box 1. High-risk glucocorticoid users

- High dose (>20 mg/d prednisone or equivalent) for ≥ 3 months
- Postmenopausal women
- High fall risk

[168] and the ability of this compound to potentially effect the central pathogenic mechanism of GIOP.

Treatment patterns and recommendations

Despite accumulating data on the effectiveness of anti-osteoporotic therapies in GIOP, only 5% to 35% of patients on glucocorticoids in the United States, Canada, and Great Britain receive therapies to prevent or treat GIOP [6,7,169–174]. Although there are many reasons for this historically low use of GIOP interventions and for the significant practice pattern variation in GIOP management, it seems that symptomatic glucocorticoid toxicities, such as mood changes, weight gain, insomnia, hypertension, and hyperglycemia, may receive more attention from some patients and physicians [175].

Box 2. Indications for other treatment options in GIOP

- Hormone replacement therapy
 - Estrogen/SERM for hypogonadal women without contraindications^a
 - Testosterone for men with low free testosterone
 - Consider combination with bisphosphonate^b
- Calcitonin
 - Bisphosphonate intolerance
 - Acute fracture pain^c
 - Thiazide diuretics
 - Consider within first 2 years of glucocorticoid use
 - Evidence of significant hypercalciuria

^a Estrogen is contraindicated in women with a history of cardiovascular disease, venous thromboembolic disease, or breast cancer. There are no data from clinical trials to directly support the use of SERMs in GIOP.

^b Combination therapy supported by limited data from postmenopausal osteoporosis clinical trials suggesting a modest synergistic benefit on BMD [178–180].

^c Based on the results of small studies suggesting analgesic benefit in the setting of acute compression fractures [181,182].

A cost effectiveness study found relatively unacceptable costs per quality adjusted life year (QUALY) gained (\$92,600 dollars US/QUALY) for invoking a strategy of screening RA patients and treating those with alendronate whose BMD *t* score was less than -1.0 [176]. Although this study highlights the possible societal pitfalls of treating very low risk patients aggressively, the analysis assumed that fracture reduction achieved with bisphosphonates for GIOP was even lower than seen in studies of postmenopausal women. Bone mass remains a critical element in predicting fracture risk, and it is difficult to accurately predict low bone mass on the basis of clinical risk factors alone [177].

Based in part on specialty society recommendations [107,108], results from large RCTs of GIOP interventions, and cost effectiveness considerations, an algorithmic approach to the evaluation and treatment of GIOP is presented in Fig. 4 and in Boxes 1 and 2. Given the accumulating data on the efficacy of bisphosphonates for preventing and treating GIOP, some authorities add a bisphosphonate immediately in all high-risk patients [111]. Although this algorithm represents a rational approach, this is a rapidly changing area, and it is anticipated that GIOP management will be further refined, based on emerging literature and societal cost-effectiveness considerations.

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