

Glucocorticoid-Induced Osteoporosis: Clinical and Therapeutic Aspects

revisão

GHERARDO MAZZIOTTI
ANDREA GIUSTINA
ERNESTO CANALIS
JOHN P. BILEZIKIAN

Department of Internal Medicine, University of Brescia (GM & AG), Italy; Saint Francis Hospital and Medical Center (EC), Hartford, CT, USA, and the University of Connecticut School of Medicine, Farmington, CT, USA; and Department of Medicine, College of Physicians and Surgeons, Columbia University (JPB), New York, NY, USA.

ABSTRACT

Glucocorticoid-induced osteoporosis (GIO) is the most common form of secondary osteoporosis. Fractures, which are often asymptomatic, may occur in as many as 30–50% of patients receiving chronic glucocorticoid therapy. Vertebral fractures occur early after exposure to glucocorticoids, at a time when bone mineral density (BMD) declines rapidly. Fractures tend to occur at higher BMD levels than in women with postmenopausal osteoporosis. Glucocorticoids have direct and indirect effects on the skeleton. They impair the replication, differentiation, and function of osteoblasts and induce the apoptosis of mature osteoblasts and osteocytes. These effects lead to a suppression of bone formation, a central feature in the pathogenesis of GIO. Glucocorticoids also favor osteoclastogenesis and as a consequence increase bone resorption. Bisphosphonates are the most effective of the various therapies that have been assessed for the management of GIO. Anabolic therapeutic strategies are under investigation. Teriparatide seems to be also efficacious for the treatment of patients with GIO. (**Arq Bras Endocrinol Metab 2007;51/8:1404-1412**)

Keywords: Osteoporosis; Fractures; Glucocorticoids therapy; Bone mineral density; Bone formation; Bisphosphonates; Teriparatide

RESUMO

Osteoporose Induzida por Glicocorticóides: Aspectos Clínicos e Terapêuticos.

A osteoporose induzida por glicocorticóides (OIG) é a forma mais comum de osteoporose secundária. Fraturas, que são freqüentemente assintomáticas, podem ocorrer em até 30–50% dos pacientes recebendo terapia glicocorticóide crônica. Fraturas vertebrais ocorrem logo após exposição aos glicocorticóides, ocasião em que a densidade mineral óssea (DMO) diminui rapidamente. As fraturas tendem a ocorrer mais com níveis elevados de DMO do que em mulheres com osteoporose da pós-menopausa. Os glicocorticóides têm efeitos diretos e indiretos sobre o esqueleto: eles impedem a replicação, a diferenciação e a função dos osteoblastos e induzem apoptose dos osteoblastos maduros e osteócitos. Esses efeitos levam à supressão da formação óssea, uma manifestação central da patogênese da OIG. Os glicocorticóides também favorecem a osteoclastogênese e, como conseqüência, aumentam a reabsorção óssea. Os bisfosfonatos são a mais efetiva das várias terapias que têm sido avaliadas para o manuseio da OIG. Estratégias terapêuticas com anabolizantes estão sendo investigadas. O teriparatídeo parece também ser eficaz no tratamento de pacientes com OIG. (**Arq Bras Endocrinol Metab 2007;51/8:1404-1412**)

Descritores: Osteoporose; Fraturas; Terapia com glicocorticóides; Densidade mineral óssea; Formação óssea; Bisfosfonatos; Teriparatídeo

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GLUCOCORTICOID-INDUCED OSTEOPOROSIS (GIO) is the most common form of secondary osteoporosis (1). Although the adverse skeletal effects of glucocorticoids have been recognized for decades, attention to GIO has increased recently because of the widespread clinical use of glucocorticoids in a variety of disorders including autoimmune, pulmonary, and gastrointestinal diseases, malignancies, and in patients receiving organ transplants. The problem has become so widely appreciated that guidelines for the prevention and treatment for GIO have been established in many countries based upon recommendations by expert scientific organizations (2). This article focuses on the clinical aspects of GIO and on the underlying pathophysiology of bone loss in this disease.

PATHOPHYSIOLOGY OF GIO

Skeletal effects of glucocorticoids

Following glucocorticoid exposure, there is a rapid, early phase of bone loss, due to excessive bone resorption, followed by a more chronic and progressive phase in which bone mass declines because of impaired bone formation (3). Glucocorticoids increase the expression of receptor activator of NF- κ B ligand (RANK-L) and decrease the expression of its soluble decoy receptor, osteoprotegerin (OPG) in stromal and osteoblastic cells (4). The combination of an increase in RANK-L, a potent activator of osteoclasts, and a reduction in OPG, an inhibitor of RANK-L action, leads to the initial phase of rapid bone loss. Glucocorticoids also enhance the expression of colony stimulating factor (CSF)-1 (5) and up-regulate receptor subunits for osteoclastogenic cytokines of the gp130 family (6). While all these actions lead to enhanced bone resorption, the central pathophysiological mechanism of GIO is reduced bone formation, due to actions to impair osteoblast differentiation and function. Glucocorticoids impair the differentiation of bone marrow stromal cells into cells of the osteoblastic lineage by diverting them, instead, toward the adipocytic lineage (7). Mechanisms involved include the induction of peroxisome proliferator activated receptor γ 2, the regulation of nuclear factors of the CAAT enhancer-binding protein family and the inhibition of Wnt/ beta-catenin signaling (8,9). Glucocorticoids also inhibit osteoblast cell differentiation through reducing the activity of bone morphogenetic protein-2 (BMP-2) (10), which plays a key role in bone formation (11). In addition to adverse effects on osteoblast differentiation, glucocorticoids inhibit osteoblast-driven synthesis of type I collagen, the major component of bone

extracellular matrix. The result is a decrease in bone matrix available for mineralization (8). The decrease in type I collagen synthesis occurs by transcriptional and post-transcriptional mechanisms (12). Glucocorticoids have pro-apoptotic effects on osteoblasts and osteocytes (13). Glucocorticoids may also affect the metabolism and function of osteocytes, modifying the elastic modulus surrounding osteocyte lacunae and causing reduced mineral to matrix ratios in the same areas with an increase in lacunar size (14). These effects of glucocorticoids on osteocytes might account for a disproportionate loss of bone strength in relation to bone mass.

In addition to the direct actions of glucocorticoids on bone-specific cells, other effects are mediated by changes in the synthesis, receptor binding or binding proteins of growth factors present in the bone microenvironment. Glucocorticoids influence primarily insulin-like growth factors (IGF). IGF-I increases the synthesis of type I collagen and bone formation, and decreases bone collagen degradation (15). Glucocorticoids suppress IGF-I gene transcription (8). The effects of glucocorticoids on IGF-I expression are reversed by PTH in vitro, an observation that may help to explain why PTH may be effective in the treatment of GIO (16). These actions are likely to be at the tissue level since it is skeletal IGF-I that is regulated by PTH and a mechanism for PTH's anabolic actions on bone (16).

EXTRASKELETAL EFFECTS OF GLUCOCORTICOIDS ON BONE METABOLISM

The main extraskeletal effects of glucocorticoids occur on calcium metabolism. In the presence of glucocorticoids, calcium absorption from the gastrointestinal tract is reduced by mechanisms that oppose vitamin D action. Moreover, glucocorticoids decrease renal tubular calcium reabsorption (1). While these actions may theoretically lead to a secondary increase in parathyroid hormone concentrations, most evidence now points away from that mechanism (18). On the other hand, there may be subtle, but important effects of glucocorticoids on PTH secretory dynamics, with a decrease in the tonic release of PTH and an increase in pulsatile bursts of the hormone (19). These changes may lead to adverse effects on bone metabolism (20), not unlike potential effects of PTH in postmenopausal osteoporosis (21). Moreover, glucocorticoids may enhance the sensitivity to PTH by changing the number of PTH receptors and their affinity for PTH (22).

However, the clinical and histomorphometric data are quite different from those associated with disorders of PTH excess. For example, GIO is associated with a preferential loss of cancellous bone whereas in hyperparathyroidism, preferential loss occurs at cortical skeletal sites (23). Histomorphometric analysis demonstrates reduced bone turnover in GIO, while in hyperparathyroidism bone turnover is enhanced (1,3).

In addition to reducing skeletal production of IGF-1, glucocorticoids exert negative effects on the growth hormone (GH)/IGF-1 axis (1). GH secretion is blunted by glucocorticoids mainly by increasing somatostatin tone in the hypothalamus (24,25), causing a state of "functional GH deficiency". Interestingly, GH suppression has been seen also in patients administered inhaled corticosteroids (25), suggesting the even topical use of glucocorticoids could have undesired skeletal consequences (26). GH and IGF-I administration has been proposed to revert some of the negative effects of chronic glucocorticoid treatment on bone (27-33). An increase in serum osteocalcin, carboxy-terminal propeptide of type I procollagen and carboxy-terminal telopeptide of type I collagen was observed following short-term recombinant human (rh)GH treatment in a selected population of patients receiving chronic corticosteroid treatment for non-endocrine diseases (27). Moreover, combined therapy of rhGH and rhIGF-I counteracted selected negative effects of glucocorticoids on bone in healthy volunteers who received short-term glucocorticoid therapy (29). Observational and controlled studies in children receiving glucocorticoid therapy for juvenile idiopathic arthritis showed that rhGH restored normal height velocity with a concomitant improvement of bone mineralization (30-33). However, the efficacy of rhGH and rhIGF-I treatment in GIO is controversial and needs to be documented by well-designed prospective controlled studies.

Glucocorticoids have also been associated with a suppressive effect on gonadal function in men and women. They inhibit follicle stimulating-hormone-induced estrogen production in women and decrease testosterone production in men. This negative effect of glucocorticoids on gonadal function may be an additional factor playing a role in the osteoporosis that follows glucocorticoid exposure (34).

EPIDEMIOLOGY OF GIO

There is a clear epidemiological association between glucocorticoid therapy and fracture risk (34-36). Fractures may occur in 30-50% of patients on chronic glu-

cocorticoid therapy (37). The vertebrae and femoral neck of the hip are specifically involved, whereas risk at the forearm, a site of cortical bone, is not increased, confirming that glucocorticoids affect predominantly cancellous bone (35). Vertebral fractures associated with glucocorticoid therapy may be asymptomatic (38). When assessed by X-ray-based morphometric measurements of vertebral bodies, more than 1/3 of postmenopausal women on chronic (> 6 months) oral glucocorticoid treatment have sustained at least 1 vertebral fracture (38). As shown in studies of subjects after cardiac transplantation, these fractures occur early, at a time when bone density may be declining rapidly (39). In this setting, therefore, fractures can occur even though the T-score *per se* may not be in the range where one would ordinarily consider the risk to be high.

Along with the demonstration that fractures can occur early in the course of glucocorticoid therapy, fracture incidence is also related to the dose and duration of glucocorticoid exposure (36). Doses as low as 2.5 mg of prednisone equivalents per day can be a risk factor for fracture, but the risk is clearly greater with higher doses. Chronic use is also associated with greater fracture risk (1,36). When daily amounts of prednisone or its equivalent exceed 10 mg on a continuous basis, and duration of therapy is greater than 90 days, the risk of fractures at the hip and vertebral sites is increased by 7- and 17-fold respectively (36). The risk of fracture declines after discontinuation of glucocorticoids although the recovery is gradual and often incomplete (1,36). With sufficiently long exposure to cumulative amounts of prednisone (i.e. > 10 g), irreversible loss of cancellous bone and of bone microarchitecture is not uncommon (36).

Most of the epidemiological data associating fracture risk with glucocorticoid administration come from the use of oral glucocorticoids. There is much less certain data about risk associated with inhaled glucocorticoids (40-45). Indeed, whether there is an increased risk of fracture in patients taking inhaled glucocorticoids is not clear since systemic absorption of the drug is exceedingly small. It is also important to bear in mind that the underlying disorder for which inhaled or systemic glucocorticoids is used may also be a cause of bone loss. The systemic release of local bone-resorbing cytokines in some of these disorders could stimulate bone loss (46,47). There are also local factors to consider. In inflammatory bowel disease, bone loss may be due, in part, to malabsorption of vitamin D, calcium and other nutrients (46). In chronic lung disease, hypoxia, acidosis, reduced physical activity, and smoking may all contribute to bone loss, independent on the use of inhaled glucocorticoids (34,45,48,49).

Individual factors are also important in determining the risk of fractures when glucocorticoids are used. The basis for such heterogeneity to glucocorticoid-associated fracture risk may be associated with polymorphisms of the *glucocorticoid receptor* gene (50,51). Another explanation for inter-individual variability among those exposed to glucocorticoids is related to differential activity of peripheral enzymes that interconvert active to inactive glucocorticoid molecules. 11β -hydroxysteroid dehydrogenases regulate the interconversion between cortisone and active cortisol. This enzyme system therefore plays a critical role in the regulation of glucocorticoid activity (52). Two distinct 11β -hydroxysteroid dehydrogenase enzymes have been described. 11β -hydroxysteroid dehydrogenase type-1 is primarily a glucocorticoid activator, converting cortisone to cortisol. This enzyme is widely expressed in glucocorticoid target tissues, including bone (52). The activity of 11β -hydroxysteroid dehydrogenase type-1 and the potential to generate cortisol from cortisone in human osteoblasts is increased by pro-inflammatory cytokines and by glucocorticoids themselves (53-55). An increase of 11β -hydroxysteroid dehydrogenase type 1 activity occurs with aging, possibly providing an explanation for the enhanced glucocorticoid effects in the skeleton of elderly subjects (55).

CLINICAL ASPECTS

Awareness of GIO

Despite the clear clinical recognition that glucocorticoids can cause bone loss and fractures, many patients receiving, or being considered for, long-term glucocorticoid therapy are not evaluated for their skeletal health. Many patients do not receive specific prophylaxis or treatment when indicated (56,57). This observation is particularly evident in males taking glucocorticoids, in accordance with the general inadequate awareness of male osteoporosis (58,59). The awareness of GIO is higher in elderly female patients (60). Less than half of glucocorticoid-treated male patients are assessed with a bone mineral density (BMD), and less than one-third receive treatment (57). Therefore, in light of the limited awareness and undertreatment of GIO, clinical detection programs have been developed. However, the results have not been encouraging (61,62). Physicians apparently do not appreciate the potential relevance of glucocorticoid use to bone loss. One hopes that well-conducted long-term "educational" programs will improve this situation (60).

DIAGNOSTIC GUIDELINES

The American College of Rheumatology (ACR) recommends a BMD measurement before starting bisphosphonates in all subjects taking glucocorticoids (63), whereas the Royal College of Physicians recommends BMD measurement only in subjects younger than 65 years (64). It is well known that the fracture threshold in GIO is much lower than in postmenopausal osteoporosis and, thus, that fractures in GIO occur at higher BMDs than in postmenopausal osteoporosis. This point has to be taken into account when treatment recommendations are made on the basis of BMD measurements (37). In fact, the intervention threshold of the Royal College of Physicians is a T-score of -1.5 and that of the ACR is a T-score of -1, both cut-points that are much higher than the T-score treatment threshold of -2.5 in postmenopausal women (63-65). The reasons for the altered relationships between BMD and risk of fracture are complex (66,67). In addition to rapid bone loss that can increase fracture risk at any T-score, fracture risk is also related to bone strength. Although an important index of bone strength, BMD does not give information about other relevant indices such as structural and material properties of bone (68). Deterioration of cancellous structure can have a major impact on fracture risk independent of BMD. In GIO, cancellous microarchitecture is adversely affected. The negative effects of glucocorticoids on osteocytes may also play a role in reduced bone strength. Reductions in trabecular thickness, number, and connectivity are not reliably measured by BMD (14). Newer technologies such as high-resolution peripheral quantitative computed tomography or microMRI may be helpful in identifying individuals on glucocorticoids whose BMD may not be low, but in whom bone quality has deteriorated (69).

The identification of pre-existing osteoporotic fractures in patients who already started glucocorticoids may be important for the decision to treat, as established by the Royal College of Physicians guidelines (64). As in other forms of secondary osteoporosis (70-72), in GIO vertebral fractures may be asymptomatic (38). Therefore, the clinical history (73) may not be reliable. Consequently, a radiological approach with morphometric analysis is useful for the identification of vertebral deformities (74).

The Royal College of Physicians guidelines recommend evaluation of calcium metabolism in all subjects (64) in order to select those for whom vitamin D and/or calcium supplementation are indicated. In

contrast, the ACR recommends a more universal approach since calcium and vitamin D are generally helpful in all patients with GIO (63,65).

The guidelines do not include the analysis of bone turnover in the skeletal assessment of patients taking glucocorticoids. In post-menopausal osteoporosis biochemical markers of bone turnover, as surrogate measures of bone remodeling activity, were found to be reliable in predicting fracture risk (75), but in GIO, data about fracture prediction using bone turnover measurement are lacking or uncertain (76).

THERAPEUTIC GUIDELINES

ACR and the Royal College of Physicians advocate the following measures for the prevention and treatment of GIO: general health awareness, administration of sufficient calcium and vitamin D, reduction of the dose of corticosteroids to a minimum and, when indicated, therapeutic intervention with bisphosphonates and other agents (37,66).

The Royal College of Physicians guidelines recommend primary prevention in all men and women over the age 65 years, in individuals with a personal and familial history of osteoporosis and in younger people with BMD T-score ≤ -1.5 SD, who are to receive at least 3 months of oral glucocorticoid therapy at any dose (64). ACR recommends a preventive approach in patients exposed to glucocorticoids for longer than 3 months (5 mg prednisone equivalent daily), including lifestyle changes, such as tobacco cessation and reduction of alcohol consumption, an exercise program, restriction of sodium intake (in presence of hypercalciuria), sufficient calcium intake and adequate vitamin D supplementation (63). ACR suggests that treatment with bisphosphonates should be started in these subjects if their T-score is below -1.0, as assessed by lumbar spine DXA (63). The selection of patients for preventive and therapeutic measures is controversial. A recent meta-analysis demonstrated that treatment of GIO is cost-effective in patients with prior fracture, in individuals aged more 75 years or in younger subjects with T-scores less than -2.0 (77). On the other hand, it was also pointed out that in aged patients with reduced life expectancy as assessed by the Quality-Adjusted Life Years (QALY) model the cost-effectiveness may be low (78), although this approach may be ethically criticized (79).

Various pharmacological agents have been assessed for prevention and treatment of GIO. It should be pointed out that the primary endpoint of

most studies was a change in BMD, whereas fracture outcomes were measured in a few studies (80-89), as secondary endpoints.

Vitamin D and calcium are recommended by both ACR and Royal College of Physicians guidelines, although the latter restrict the administration to patients with vitamin D insufficiency and/or with inadequate calcium intake (63-65). Vitamin D and its analogues prevent bone loss during glucocorticoid therapy (91,92). Alfacalcidol, a vitamin D analogue, is said to have dual effects on bone by increasing bone formation and reducing bone resorption (92). Alfacalcidol suppresses the synthesis and release of parathyroid hormone and increases the intestinal absorption of calcium and its reabsorption in the distal renal tubule (93). In addition to its role in calcium homeostasis, vitamin D increases muscle strength (80). In a 2-year randomized trial, subjects with rheumatoid arthritis receiving prednisone therapy (mean dose 5.6 mg/day) BMD fell at a rate of 2.0% and 0.9% per year in the lumbar spine and trochanter, respectively. In contrast, patients randomized to calcium (1000 mg/day) and vitamin D (500 IU/day) gained BMD at an annual rate of 0.72% at the spine and 0.85% in the trochanter (94). A practical point of vitamin D therapy in subjects receiving glucocorticoids relates to vitamin D resistance that is often seen in this setting. Rather than maintaining 25-hydroxyvitamin D levels at a minimally adequate level, 30 ng/ml (82 nmol/L), many experts recommend that the goal be set at 40-60 ng/ml. In order to maintain these levels, patients often require amounts of 1,000-2,000 IU of vitamin D3 daily (95).

Bisphosphonates are considered to be the gold standard for the prevention and treatment of GIO (2,65). Both ACR and Royal College of Physicians guidelines point out the efficacy of these drugs (63-65), although the ACR guidelines are more explicit in recommending these agents as first-line therapy (63,65). Available data are for risedronate and alendronate, although newer bisphosphonates have been recently tested with encouraging results (96). The benefits of bisphosphonates in GIO have been ascribed primarily to their antiresorptive effect, although an inhibition of glucocorticoid-induced apoptosis of osteoblasts and osteocytes may contribute to the therapeutic effects of bisphosphonates (34). Bisphosphonates are more effective than vitamin D in the prevention of fractures in GIO, but should be given with supplemental calcium and vitamin D (80). A meta-analysis concluded that bisphosphonates are the most effective of the various therapies that have been assessed for

the management of GIO (34,80). An overall reduction in risk of morphometric radiological vertebral deformities of 37% (relative rate 0.63, 95% confidence interval 0.49–0.80) was reported (34). The use of bisphosphonates in eugonadal premenopausal women has to be carefully considered, due to unknown consequences of these drugs on pregnancy and fetal development.

If not contraindicated, hypogonadism should be treated in men as well as in women (65). Estrogens preserve bone mass in postmenopausal women regardless of whether glucocorticoids are being used (97). It seems reasonable to consider estrogen therapy as long as there are no contraindications (98).

Current guidelines do not yet include any anabolic approach for the treatment of GIO, although anabolic therapy would appear to have promise since the disorder is primarily one of reduced bone formation. PTH is an attractive candidate because it protects against osteoblast apoptosis (99,100) and increases osteoblast cell number (101). The use of PTH in GIO has been examined in postmenopausal women with rheumatoid arthritis taking prednisone and estrogens (102-104). In this population, daily treatment with PTH (1-34) increased spinal BMD. Modest increases in bone mass were observed at the hip. PTH administration induces an initial uncoupling of bone remodeling with an early increase in bone formation followed by a more gradual increase of bone resorption (105). According to the concept of the “anabolic window”, PTH rapidly stimulates osteoblast function, inducing an up-regulation of osteoblast cytokines such as sRANKL, IL-6, and a suppression of OPG (105). These actions eventually lead to osteoclast activation and gradual rebalancing of bone formation and resorption. Recently, a multicenter, randomized controlled study was performed to compare the effects of teriparatide [PTH(1-34)] with those of alendronate on lumbar spine BMD density in patients with GIO. Vertebral and nonvertebral fractures were secondary outcomes. Teriparatide had a greater effect on BMD than alendronate. In addition, teriparatide increased serum markers of bone turnover, such as N-terminal extension peptide of type 1 collagen and C-terminal telopeptide of type 1 collagen. As expected, alendronate reduced biochemical markers of remodeling. Teriparatide had a greater impact to reduce vertebral fractures than alendronate ($P = 0.004$). Nonvertebral fractures were not different between the teriparatide and alendronate treatment groups (5.6% vs. 3.7%, respectively), as was the case for nonvertebral fragility fractures (2.3% vs. 1.4%). There were no specific dif-

ferences in rates of adverse events between teriparatide and alendronate. These results would confirm the hypothesis that teriparatide is efficacious for the treatment of patients with GIO (106).

SUMMARY

Glucocorticoids are an important therapy for a variety of disorders but this therapy carries with it unwanted adverse effects such as bone loss. The pathophysiology of GIO points to a major effect to reduce processes associated with bone formation although increased bone resorption is also seen particularly in the early stages. Subjects on glucocorticoids often have disorders that themselves are associated with bone loss independent of the use of glucocorticoids. The predictable GIO-associated loss in bone mass and in bone quality has led many authoritative bodies such as the ACR and the Royal College of Physicians to recommend guidelines for evaluation and therapy. Intervention is recommended in subjects whose BMD is not at the classical osteoporotic level because fractures occur at higher BMD than is typical for postmenopausal women. This is due to deleterious effects on bone quality that are not routinely measured by currently available imaging modalities. Along with sufficient calcium, vitamin D, and life style modification, bisphosphonates can be very effective.

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Address for correspondence:

John P. Bilezikian
 Department of Medicine
 Columbia University College of Physicians and Surgeons
 630 W. 168th Street
 New York, NY 10032
 Fax: 212.305.6486
 E-mail: jpb2@columbia.edu