Glucocorticoid-Induced Osteoporosis: Summary of a Workshop

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Bone remodeling is regulated by systemic and local factors, and glucocorticoids are hormones with a significant impact on the skeleton. Bone remodeling is tightly regulated, and bone formation occurs in areas of previously resorbed bone. Bone is continuously regenerated, a process that is carried out by basic multicellular units. These units are comprised by teams of juxtaposed osteoclasts and osteoblasts. These bone-resorbing and -forming cells maintain bone remodeling in an orderly fashion, and osteoclastogenesis is dependent on the genesis and presence of osteoblasts. The number of bone-forming and bone-resorbing cells present in the basic multicellular units is also dependent on an orderly cellular death or apoptosis. Therefore, cell genesis and death are critical for the maintenance of bone homeostasis. The genesis of osteoblasts and osteoclasts is governed by specific genes, local regulatory factors, and various systemic hormones, including glucocorticoids (1).

Mechanisms of glucocorticoid action in bone

Glucocorticoids decrease gastrointestinal calcium absorption, which may result in modest elevations in serum levels of PTH. However, these do not reach the hormonal levels observed in hyperparathyroidism, and the skeletal changes of glucocorticoid-induced osteoporosis (GIO) cannot be explained by excess PTH. In contrast to the changes observed in postmenopausal osteoporosis and hyperparathyroidism, where increased bone resorption prevails, bone histomorphometric analysis of patients exposed to glucocorticoids reveals only modest increases in bone resorption. Biopsies from patients with GIO display a marked depression of osteoblastic function and mineral apposition rates, whereas in postmenopausal osteoporosis and hyperparathyroidism there is no decrease in bone formation (2, 3). It is possible that the modest changes in osteoclastic resorption found in GIO are transient. Chronic treatment with glucocorticoids causes a redistribution of spontaneous PTH secretion, reducing the tonic and increasing the pulsatile release of PTH (4). This altered PTH secretion could play a secondary role in the pathophysiology of GIO.

It is now apparent that most of the skeletal changes in GIO are due to direct actions of glucocorticoids in skeletal cells. Glucocorticoids regulate gene expression by transcriptional and posttranscriptional mechanisms. The transcriptional effects have been studied in greater detail, are mediated by the GR, and occur by activation or repression of gene expression (5). Activation requires the DNA binding of a receptor dimer to cognate elements in the promoter of target genes, whereas repression is mediated predominantly by protein/protein interactions between the receptor monomer and transcription factors. To discriminate the different modes of glucocorticoid action in development and physiology, mice carrying a DNA binding defective glucocorticoid receptor have been created (6, 7). In contrast to mutants with a disrupted GR gene, mice carrying a DNA binding defective glucocorticoid receptor are viable after birth, but trans-activation functions of the GR are absent. The model allows discrimination between DNA binding-dependent and -independent functions of the GR, responsible for a specific activity (6, 7). Another useful model is based on the use of targeted gene inactivation, which allows for the tissue-specific excision of a selected gene (8). Bacteriophage P1 Cre recombinase is a 38-kDa protein that recognizes the 34-bp DNA sequenceloxP (locus of crossover P1), and whenloxP sites flank a gene region, Cre induces an intramolecular recombination and excision of the intervening DNA (9). This results in deletion of the DNA sequence flanked byloxP. By placing the Cre recombinase under the control of a tissue-specific promoter, the function of a gene can be examined specifically in that tissue and can be inactivated at an opportune time. For this purpose, transgenic mice overexpressing the Cre recombinase, under the control of a tissue-specific promoter, are mated with mice in which a specific gene is flanked byloxP sequences. The progeny will carry the tissue-specific gene deletion. Using this model, the GR gene has been inactivated selectively in liver, thymus, monocytes/macrophages, and brain, respectively, but targeted inactivation in skeletal tissue has not been carried out (10). This will be required to define the physiological role of glucocorticoids in bone. Levels of expression of the GR may modulate glucocorticoid action in bone, and selected cytokines, such as IL-6 and IL-11, respectively, increase and decrease GR levels, possibly sensitizing or desensitizing osteoblastic cells to the effects of glucocorticoids (11).

Although the fundamental action of glucocorticoids in bone occurs by decreasing bone formation, in vivo findings in animals and humans are consistent with an early increase in bone resorption after exposure to glucocorticoids. This is probably responsible for the rapid bone loss observed in humans after the initiation of glucocorticoid therapy and also explains the effectiveness of antiresorbing agents in the management of GIO. Recent interest has focused on the glucocorti-
...ticoid effects on the receptor activator of the nuclear factor-κB ligand (RANK-L)-OPG axis. These are osteoblastic signals that are final mediators of osteoclastogenesis. RANK-L, in the presence of colony-stimulating factor-1, induces osteoclastogenesis, whereas OPG acts as a soluble decoy receptor for RANK-L, preventing its effects in bone (12). Glucocorticoids enhance RANK-L and colony-stimulating factor-1 expression and inhibit OPG production with a consequent induction of osteoclastogenesis (13, 14). These findings provide a mechanism for the early increase in bone resorption in GIO. Eventually, there is a state of decreased bone remodeling. This is secondary to a decline in the number of mature osteoblasts, with a consequent decrease in osteoblastic signals required for osteoclastogenesis. There is additional evidence for glucocorticoid effects on bone resorption, as these steroids enhance the expression of collagenase-3, a metalloprotease that plays a central role in bone resorption (15, 16). The stimulatory effect of glucocorticoids on collagenase expression occurs in osteoblastic cells by posttranscriptional mechanisms (15). These result in stabilization of the collagenase-3 transcript, an effect that is secondary to the induction or activation of cytosolic proteins that bind to specific regions of the 3′-untranslated region of the collagenase-3 RNA. This region contains seven AU-rich elements, which are AUUUA motifs and are often implied in the regulation of transcript stability (17).

Central to the pathogenesis of GIO are the effects of glucocorticoids on bone formation (18). These are secondary to a decrease in osteoblastic cell number and activity. Recent evidence indicates that a decrease in osteoblastogenesis combined with an increase in the apoptosis of mature osteoblasts and osteocytes are causes of the decreased number of osteoblasts and are central to the pathophysiological changes of GIO (18–20). The decrease in osteoblastogenesis is accompanied by an increase in adipogenesis, explaining the increased adiposity of the bone marrow of patients exposed to glucocorticoid excess (21). Even though glucocorticoids increase the apoptosis of fully formed mature osteoblasts, this is not the case in immature cells. This is in part because glucocorticoids have complex effects on osteoblast generation and death. For example, when primary rat osteoblasts are cultured under differentiating conditions in the absence of cortisol, the cells differentiate, mineralize, and undergo apoptosis. The addition of cortisol results in a decrease in cell differentiation, so that cells do not mature, mineralize, and die. Consequently, the lack of terminal cell differentiation under these experimental conditions results in decreased cellular death (22). The decrease in osteoblastic maturation is in accord with the inhibitory effects of glucocorticoids on the differentiated function of the osteoblast (18).

Selected inhibitory actions of glucocorticoids on bone formation are secondary to the regulation of the IGF axis (23). IGF-I has stimulatory effects on bone formation, opposite those of glucocorticoids, and IGF-I levels are decreased by cortisol. Glucocorticoids inhibit IGF-I gene transcription by regulating a family of CCAAT enhancer-binding proteins, which, in the presence of glucocorticoids, are induced and bind to a specific site adjacent to the third start site of transcription of the IGF-I exon 1. This results in an inhibition of IGF-I transcription (24). Glucocorticoids also regulate various IGF-binding proteins. Glucocorticoids inhibit the transcription of IGF-binding protein-5, a binding protein reported to have stimulatory effects on bone formation (25). These newer insights into the pathogenesis of GIO may support the use of intermittent PTH administration as anabolic therapy. PTH increases the skeletal levels of IGF-I and opposes the inhibitory effects of glucocorticoids on IGF-I production and apoptosis (18). Glucocorticoids have additional inhibitory effects on the GH-IGF-I axis, and patients exposed to these steroids have blunted GH responses to GHRH (26). This subclinical hyposomatotropism could play an additional role in the decreased bone formation, even though serum IGF-I levels in GIO are essentially normal. It is conceivable that skeletal IGF-I, which is in part GH dependent, plays a role in the effect observed. This would be supported by data demonstrating that GH receptor null mice develop osteopenia, which is reversed by the systemic administration of IGF-I (27).

Clinical features of GIO and conditions leading to GIO

Patients exposed to glucocorticoids in excess have decreased bone mineral density (BMD), and 30–50% develop vertebral fractures. The degree of bone loss is related to the dose and duration of therapy, although prolonged exposure to modest, frequently considered physiological doses of glucocorticoids results in an increased risk of fractures (28). Patients with GIO lose more trabecular than cortical bone; consequently, they have a greater risk of bone loss in the spine than in the hip. After initiation of corticosteroid therapy, there is a phase of rapid bone loss, followed by a slower, but continuous, decline in BMD. Although BMD is low in GIO, after an initial rapid loss of bone there is a stabilization of BMD that could give a false sense of reassurance to physicians caring for patients receiving long-term glucocorticoid treatment. The stabilization of BMD should not preclude the need for aggressive therapy, because these patients are at an added risk of fractures. Biochemical markers of bone turnover may be altered in patients with Cushing’s syndrome or patients exposed to glucocorticoids. Patients chronically exposed to glucocorticoids have decreased serum osteocalcin and alkaline phosphatase levels, but do not have elevated urinary free deoxypyridinoline excretion (29). These observations are in accordance with the predominant inhibitory effect of glucocorticoids on bone formation.

Postmenopausal women are at greater risk to develop osteoporosis after glucocorticoid exposure, although the disease also affects men. In the United States, 20% of the osteoporotic population is male (30). The pathogenesis of GIO in males and females is probably similar, and most of the studies analyzing the results of therapy for GIO have not distinguished between men and women. In those situations where both genders were analyzed separately, there was a tendency for the therapeutic intervention to be less dramatic in men than in women, but this may have been more a matter of the smaller number of men treated, which typically constituted one third of the therapeutic cohort. Nevertheless, the data argue that men as well as women develop GIO, and the effective therapeutic approaches for women are applicable to men. This concept is also supported by the effectiveness of
Antiresorptive and anabolic therapy in men with idiopathic osteoporosis, which is similar to that observed in women (31, 32).

Accelerated bone loss is a significant clinical problem of patients undergoing kidney, liver, and heart and lung transplantation (33). Glucocorticoids and other immunosuppressive agents are likely to be major contributory factors to the bone disorder. Hypogonadism, vitamin D deficiency, malnutrition, reduced physical activity, impaired renal function, and preexisting bone disease also play a role in the pathogenesis of osteoporosis after organ transplantation. The highest rates of bone loss are observed during the first few months after transplantation, with a tendency for bone mass to recover subsequently. Fractures occur at unusual sites, and fracture incidence is highest in the first year after transplantation. Management of osteoporosis after transplantation includes optimization of bone health before surgery and prevention of bone loss posttransplantation. Trials on the use of intermittent iv pamidronate therapy in patients exposed to glucocorticoids and undergoing heart and lung transplantation have shown beneficial effects (34, 35). However, there have been no randomized controlled trials with fracture prevention as the primary end point. In the future, modification of immunosuppressive regimens and the use of bisphosphonates may prove beneficial in reducing the incidence of osteoporosis and fractures after transplantation.

Rheumatological diseases are often treated with glucocorticoids, and patients suffering these disorders develop osteoporosis (36). Patients with rheumatoid arthritis develop osteoporosis, which is more evident at the hip and the radius than at the spine. The most important determinants of bone loss are disability, local disease activity, and cumulative corticosteroid dose. Juxta-articular bone loss is an early sign of the disease and precedes the development of erosions. It is likely that T cell-derived cytokines, particularly RANK-L, play a role in the bone loss of experimental arthritis and human rheumatoid arthritis (37, 38). Glucocorticoids have an added negative impact in bone homeostasis, and patients with rheumatoid arthritis treated with glucocorticoids have lower BMD than untreated patients. Bone loss in patients with systemic lupus erythematosus (SLE) is a growing problem, because the survival of patients with SLE is increasing, and they are expected to reach an older age. The bone loss is secondary to the disease itself and to agents used in its treatment. Disease-dependent mechanisms include reduced physical activity due to long-standing disabling arthritis and myopathy, renal failure, hypogonadism, the systemic effect of proinflammatory bone-resorbing cytokines, and subtle vitamin D deficiency due to sun avoidance. BMD is significantly reduced even in premenopausal women with SLE, and patients with SLE are more prone to sustain fractures than the general population (39, 40). Patients with SLE have a higher incidence of osteopenia even if they are not treated with glucocorticoids. However, corticosteroids as well as the use of azathioprine, cyclophosphamide, and cyclosporin play a role in the development of the bone disease. The available data suggest that patients with SLE and osteoporosis can derive benefits from antiresorptive therapy (40).

Patients with a variety of pulmonary disorders, such as asthma, chronic lung disease, and sarcoidosis, are frequently treated with glucocorticoids and develop osteoporosis (28, 41). Whenever possible, inhaled steroids should be used due to their lesser negative impact on bone loss than systemic glucocorticoids. Patients with sarcoidosis frequently develop osteoporosis, and approximately 40% have osteoporosis of the spine or hip. The etiology is multifactorial, including chronic glucocorticoid therapy and various degrees of hypogonadism.

Although most patients developing GIO do so because of the systemic administration of glucocorticoids, patients with endogenous Cushing’s syndrome have long been known to develop osteoporosis (42). It is important to note that patients with adrenal incidentalomas are not at an increased risk of osteoporosis, probably due to the lack of significant hypercortisolism (43).

**Prevention and treatment of GIO**

The ultimate goal in the management of GIO is the prevention of fractures. Consequently, assessment of the therapeutic efficacy of various agents in patients exposed to glucocorticoids should include their impact on bone mass and fracture risk. Because glucocorticoids decrease intestinal calcium absorption and increase urinary calcium excretion, it is appropriate that prevention measures include calcium (1500 mg daily) and vitamin D (800 IU daily), a recommendation recently made by the American College of Rheumatology. Studies of the use of calcium and vitamin D in GIO are limited, and these agents are more effective when given in conjunction with antiresorptive therapy (44). E preserve bone mass in postmenopausal women regardless of whether the women are receiving chronic glucocorticoid therapy. However, prospective data on their impact on fracture risk are lacking. Raloxifene, a selective ER modulator, increases bone mass and decreases vertebral fracture risk in postmenopausal women, but little is known about its impact on GIO. Although postmenopausal women who are E deficient and receiving glucocorticoid therapy may benefit from E or raloxifene, results are not available, and alternative therapies should be considered. Premenopausal women exposed to glucocorticoids who remain eugonadal may not require aggressive therapy, as endogenous E appear to offer bone-protective effects. Furthermore, therapies such as raloxifene and bisphosphonates could have unwanted fetal effects and are not indicated in women with childbearing potential.

The early effect of glucocorticoids to increase bone resorption justifies the use of antiresorptive therapy, and various trials on the use of oral bisphosphonates, such as alendronate, risedronate, and etidronate, have proven effective for the prevention and treatment of GIO (45). A recent study demonstrated the effectiveness of alendronate in the prevention and treatment of GIO. Nearly 500 patients exposed to glucocorticoids for periods of less than 4, 4–12, and more than 12 mo were given alendronate or placebo (calcium and vitamin D supplement) for 1 or 2 yr. Alendronate increased BMD and decreased the incidence of vertebral fractures after 2 yr (46). The beneficial effect of alendronate was more apparent in postmenopausal women, because premenopausal women treated with placebo appeared reasonably well pro-
lected from the deleterious effects of glucocorticoids. Recent studies also have documented beneficial effects of risedronate in the prevention and treatment of GIO (47, 48). Approximately 500 patients receiving glucocorticoids were enrolled in 2 clinical studies with similar protocols and with BMD and fracture rates as primary end points. The “prevention” study enrolled patients who had been receiving glucocorticoid therapy for 3 months or less, and the “treatment” study for 6 months or longer. Patients received placebo or risedronate for 1 yr while continuing glucocorticoid therapy. In the prevention study BMD declined in patients receiving placebo (calcium), an effect that was opposed by risedronate. In the treatment study BMD did not decline in the placebo (calcium and vitamin D) group and was significantly increased in the risedronate-treated group. A significant reduction in vertebral fractures was observed with risedronate when data from the 2 studies were pooled. In patients unable to receive oral bisphosphonates, their iv administration may be considered. Prospective trials on the use of iv ibandronate and pamidronate have demonstrated stabilization and increases in vertebral and hip BMD in patients with GIO. The intermittent administration of pamidronate prevented bone loss in patients exposed to glucocorticoids (34).

Anabolic agents may also play a role in the treatment of GIO. The number of studies of the efficacy of sodium fluoride in GIO is limited, and there is no apparent indication for sodium fluoride in this bone condition. New data on the use of PTH in postmenopausal osteoporosis and GIO are encouraging and suggest a potential role for this hormone in the treatment of these disorders (49, 50). PTH increases bone mass due to a selective increase in bone-forming surfaces associated with a stimulation of the differentiated function of the osteoblast, probably due to an increase in IGF-I synthesis (51). When PTH is given by continuous infusion, both osteoclastic resorption and osteoblastic formation are stimulated with a net bone loss. In contrast, when PTH is given intermittently, bone mass and strength are increased, and a reduction in vertebral fractures is observed (32, 49, 52). The impact of PTH on GIO was examined in a group of postmenopausal women with osteoporosis receiving glucocorticoids and E replacement (50). Patients were continued on glucocorticoids and assigned to either PTH and E or E replacement alone for 12 months. Spine BMD increased by 11.8% after 12 months of PTH treatment compared with that after E treatment. The effect was sustained for 12 months after discontinuing PTH, although patients continued E therapy, which should stabilize BMD.

**Recommendations**

The American College of Rheumatology and the UK Consensus Group in Management of GIO have and continue to offer updated guidelines for the prevention and treatment of GIO (53, 54). The current recommendations by the American College of Rheumatology include supplementation with calcium (1500 mg daily) and vitamin D3 (800 IU daily), the use of a bisphosphonate (alendronate or risedronate) for prevention of bone loss and fractures in any patient taking prednisone (5 mg/d) for more than 3 months, replacement of gonadal sex steroids if deficient, and consideration of the use of calcitonin if bisphosphonates are contraindicated or not tolerated. Future developments in the pathogenesis and management of GIO should offer additional guidance and a better outcome for patients exposed to glucocorticoids.

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**References**

12. Suda T, Takahashi N, Udagawa N, Jini E, Gillespie MT, Martin TJ 1999 Modulation of osteoblast differentiation and function by the new members of the tumor necrosis factor receptor and ligand families. Endocr Rev 20:345–357
16. Zhao W, Byrne MH, Boyce BF, Krane SM 1999 Bone resorption induced by

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parathyroid hormone is strikingly diminished in collagenase-resistant mutant mice. J Clin Invest 103:517–524