COMMENTARY

Should Bisphosphonates Be Used for Long-Term Treatment of Glucocorticoid-Induced Osteoporosis?

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Introduction

Skeletal mass is a reflection of the relative activities of bone-synthesizing osteoblasts and bone-resorbing osteoclasts. When the activity of osteoclasts supersedes that of osteoblasts, bone loss occurs, which, if profound, eventuates into osteoporosis (1). Although all patients with osteoporosis are predisposed to fractures, the causes of osteoporosis are many, the most common attending menopause. Estrogen deficiency typically prompts a high-turnover form of osteoporosis in which both bone formation and bone resorption are accelerated, but the relative activity of osteoclasts is greater than that of osteoblasts (2,3). Thus, suppression of osteoclasts using hormone replacement therapy was the standard of care for decades. Because of the realization that estrogens increase the risk of breast cancer and cardiovascular complications in older women, bisphosphonates have become the most common treatment of postmenopausal osteoporosis. Given the absolute increase in osteoclast activity in patients with estrogen-deficient osteoporosis, the effectiveness of bisphosphonates is not surprising. Treatment with alendronate, for example, maintains bone mass and reduces the risk of fracture in postmenopausal women with osteoporosis for as long as a decade, with minimal complications in the great majority of patients (4).

Glucocorticoid-induced osteoporosis

The most common secondary form of osteoporosis is that induced by glucocorticoids, but the skeletal dynamics of glucocorticoid-induced osteoporosis are distinctly different from those associated with estrogen deprivation. Whereas bone formation is enhanced following menopause, inhibition of osteoblasts by glucocorticoids is a major cause of progressive bone loss (5–8). The dynamics of bone resorption under the influence of glucocorticoids are, however, more complex. Upon initiation of glucocorticoid therapy, bone resorption is accelerated. The fact that administration of low-dose glucocorticoids to healthy women immediately suppresses bone degradation, as determined by urinary excretion of free deoxypyridinoline (9), suggests that the early acceleration of bone resorption observed during treatment of patients with osteoporosis may represent persistence of the effects of osteoclast-activating inflammatory cytokines (10–12). It is during this early stage in the natural history of glucocorticoid-induced osteoporosis that the combination of reduced bone formation and accelerated bone resorption yields the most profound bone loss (13,14).

The misconception that glucocorticoids accelerate osteoclast activity, regardless of the duration of treatment, forms the theoretical basis for the recommendations of the American College of Rheumatology (15), the Royal College of Physicians (16), and essentially all international guidelines, that bisphosphonates should be routinely administered for the prevention and treatment of glucocorticoid-induced osteoporosis. In fact, during long-term therapeutic exposure to steroids, bone resorption changes from accelerated to diminished, likely due to direct suppression of osteoclasts via inhibition of calpain 6 (6,8,17,18). Supporting this contention, prolonged glucocorticoid treatment dampens expression of the key osteoclastogenic transcription factor, nuclear factor of activated T cells c1 (19). In contrast to high-turnover postmenopausal osteoporosis, chronic glucocorticoid-induced osteoporosis is, therefore, a low-turnover form of the disease in which both bone formation and bone resorption are suppressed, although for-
mation is suppressed more than resorption. Importantly, the efficacy of bisphosphonates in preventing bone loss is substantially greater in the setting of high-turnover as compared with low-turnover osteoporosis (20).

Clearly, bisphosphonate therapy for at least 24 months is moderately successful in preventing bone loss and reducing the incidence of vertebral fractures in glucocorticoid-treated patients (21–23). The impact of long-term administration of bisphosphonates on the steroid-exposed skeleton is, however, unknown. Furthermore, the pharmacology of bisphosphonates raises concerns about their long-term use in the context of glucocorticoid treatment. Bisphosphonates bind bone mineral with high affinity and remain within the skeleton until they are mobilized by osteoclasts, which they inactivate, forming the basis of their skeleton-sparing properties (24). Thus, one may expect the persistence of bisphosphonates in bone for years, particularly in patients with low-turnover osteoporosis, in whom osteoclast function is diminished (25).

Fracture risk, skeletal remodeling, and bone quality

Clinical assessment of fracture risk typically involves densitometric measurement of bone mass. Densitometric analysis, however, does not consider another critical component of skeletal integrity, namely, bone quality, which is the relationship of bone mass to biomechanical strength (26). Hence, impaired bone quality is manifest by an increased predisposition to fracture at a given bone mineral density.

Skeletal remodeling is the key event regulating bone mass and likely bone quality (26). This ever-occurring process is characterized by tethering of the activities of bone resorption and formation. Remodeling is initiated by osteoclast activity. In consequence, arrested resorption dampens formation. Glucocorticoids suppress osteoblasts directly (6) and probably by inhibiting remodeling (17).

Perhaps the most important function of skeletal remodeling, however, is to replace effete bone with new bone (26). Thus, arrested skeletal remodeling, which is exemplified by the adynamic form of renal osteodystrophy, diminishes bone quality and disassociates bone mass from structural stability (26,27). Long-established glucocorticoid-induced osteoporosis reflects not only diminished bone mass but also impaired bone quality (28).

Bisphosphonates also compromise bone quality (26,29,30). Reflecting the antiremodeling properties of bisphosphonates, skeletal microdamage is substantially increased in bisphosphonate-treated animals, and the drugs also reduce bone toughness. In most individuals with postmenopausal osteoporosis, increased bone mass appears to compensate for these negative effects, at least for the first decade of treatment with antiresorptive agents (4).

Treatment of glucocorticoid-induced osteoporosis

Given the skeletal dynamics of glucocorticoid-induced osteoporosis, its treatment is complex. Antiresorptive therapy alone is logical within the first year or 2 of glucocorticoid administration, whereas osteoclast activity is accelerated, and increased bone mass appears to compensate for altered bone quality. In the chronic low-turnover phase of osteoporosis, steroids continue to suppress bone formation but also directly inhibit osteoclasts, often resulting in a virtual cessation of skeletal remodeling. Recent information suggests that bisphosphonates should be used cautiously in patients receiving more prolonged glucocorticoid treatment. Specifically, a number of bisphosphonate-treated patients in whom osteonecrosis of the jaw developed were exposed to systemic steroids (31). Furthermore, investigators have reported atypical, poorly healing fractures, particularly of the femoral shaft, in bisphosphonate-treated patients (32). Interestingly, bone biopsies of these individuals often demonstrate suppressed remodeling, and several of the patients were receiving glucocorticoids (33–35).

Anabolic drug therapy

Caution about the prolonged use of bisphosphonates is complemented by the greater success of the bone anabolic drug, teriparatide, in terms of increasing bone mineral density and preventing vertebral fractures. In a randomized, double-blind trial (22), teriparatide or alendronate was administered to glucocorticoid-treated patients, most of whom were postmenopausal women with rheumatic disease. In contrast to the suppressive effects experienced by patients receiving alendronate, those receiving teriparatide experienced accelerated bone remodeling. In a 36-month continuation study, the anabolic effects of teriparatide persisted, as reflected by increased bone mineral density, decreased occurrence of vertebral fractures, and slight but significantly sustained increases in markers of bone formation (36,37). As demonstrated in a recent post hoc analysis, the glucocorticoid dose affects these responses (38).

The use of teriparatide in glucocorticoid-induced osteoporosis is compromised, however, by cost, the
absence of long-term data due to restricted duration of administration, and the potential plateauing of anabolic action. Thus, from a public health perspective, strategies involving the use of antiresorptive agents are presently necessary. The results of recent clinical trials indicate that 12 months of treatment with denosumab, a humanized monoclonal antibody targeting the osteoclast-stimulating cytokine RANKL, effectively reduces glucocorticoid-induced osteoporosis in patients with rheumatoid arthritis (39). In contrast, the suppression of bone remodeling by denosumab is more profound than suppression by bisphosphonates (40). Therefore, prolonged administration of denosumab to glucocorticoid-treated patients also deserves vigilance. Further comparative effectiveness studies, which ideally are sufficiently large and long enough to fully understand the fracture risk at both vertebral and nonvertebral sites, are needed to better discern the benefits of antiresorptive and anabolic agents in the long-term management of glucocorticoid-induced osteoporosis.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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