GLUCOCORTICOID INDUCED OSTEOPOROSIS

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SUMMARY – Glucocorticoid therapy is the most common cause of secondary osteoporosis and the leading iatrogenic cause of the disease. Often, the presenting manifestation is fracture, which occurs in 30% to 50% of patients receiving long-term glucocorticoid therapy. Glucocorticoid-induced osteoporosis predominantly affects regions of the skeleton that have abundant cancellous bone such as lumbar spine and proximal femur. Progress has been made in clarifying the pathophysiological mechanisms that result in glucocorticoid-induced osteoporosis. Although the options for prevention and treatment of glucocorticoid-induced osteoporosis continue to expand, provider compliance with preventive measures remains suboptimal.

Key words: *Glucocorticoids; Therapy; Secondary osteoporosis*

Introduction

Synthetic glucocorticoids (GC) are used in a wide variety of disorders, including autoimmune, pulmonary and gastrointestinal diseases, as well as in patients following organ transplantation and those with malignancies. Although the indications for glucocorticoids in these various conditions are clear, their use is fraught with a host of potential side effects. The use of GC, however, is associated with a variety of adverse effects, including development of osteoporosis and fractures[1]. In patients who have received GCs for longer than six months, the estimated glucocorticoid-induced osteoporosis (GIO) frequency is 50%[2]. One-third to one-half of long-term GC users may develop fractures. Furthermore, the risk of fractures strongly correlates with the daily and cumulative dose of GC and does not seem to correlate with the specific underlying disease[3]. The underlying diseases for which GCs are prescribed, however, usually carry a risk of osteoporosis. 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[4]. 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[5,6]. Thus, suppression of osteoclasts using hormone replacement therapy was the standard of care for decades. This article focuses on the cellular aspects of glucocorticoid action in bone, highlighting the mechanisms that are responsible for bone loss. We also review current guidelines and therapeutic approaches for the prevention and treatment of GIO.

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Glucocorticoid-Induced Osteoporosis

The most common secondary form of osteoporosis is that induced by GC, but the skeletal dynamics of GIO is distinctly different from that associated with estrogen deprivation. Whereas bone formation

is enhanced following menopause, the inhibition of osteoblasts by GC is a major cause of progressive bone loss[7-10]. The dynamics of bone resorption under the influence of GCs is, however, more complex. Upon initiation of GC therapy, bone resorption is accelerated. The fact that administration of low-dose GC to healthy women immediately suppresses bone degradation, as determined by urinary excretion of free deoxypyridinoline[11], 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[12-14]. It is during this early stage in the natural history of GIO that the combination of reduced bone formation and accelerated bone resorption yields the most profound bone loss[15,16]. 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[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 GIO is, therefore, a low-turnover form of the disease in which both bone formation and bone resorption are suppressed, although formation 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].

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[21]. Skeletal remodeling is the key event regulating bone mass and likely bone quality[21]. 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. GCs suppress osteoblasts directly and probably by inhibiting remodeling[17]. Perhaps the most important function of skeletal remodeling, however, is to replace effete bone with new bone[21]. Thus, arrested skeletal remodeling, which is exemplified by the adynamic form of renal osteodystrophy, diminishes bone quality and disassociates bone mass from structural stability[21,22]. Long-established GIO reflects not only diminished bone mass but also impaired bone quality[23].

Treatment of Glucocorticoid Induced Osteoporosis

Given the skeletal dynamics of GIO, its treatment is complex. Because GCs induce an overall negative calcium balance, adequate calcium and vitamin D supplementation is important. A Cochrane Database Meta-Analysis concludes that calcium and vitamin D supplementation should be started in all patients who are administered GCs because of their low toxicity, low cost and the possible benefit in terms of fracture risk[24]. Vitamin D is a hormone that increases intestinal calcium absorption and increases its reabsorption in distal renal tubules. Antiresorptive therapy alone is logical within the first year or two of GC 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 virtual cessation of skeletal remodeling. Recent information suggests that bisphosphonates should be used cautiously in patients receiving more prolonged GC treatment. Specifically, a number of bisphosphonate-treated patients in whom osteonecrosis of the jaw developed were exposed to systemic steroids[25]. Furthermore, investigators have reported atypical, poorly healing fractures, particularly of the femoral shaft, in bisphosphonate treated patients[26]. Interestingly, bone biopsies of these individuals often demonstrate suppressed remodeling, and several of the patients were receiving GCs[27-29].

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[30], teriparatide or alendronate was administered to GC 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[31,32]. As demonstrated in a recent *post hoc* analysis, the GC dose affects these responses[33]. The results of recent clinical trials indicate that 12-month treatment with denosumab, a humanized monoclonal antibody targeting the osteoclast stimulating cytokine RANKL, effectively reduces GIO in patients with rheumatoid arthritis[34].

Conclusion

GIO is a serious skeletal disorder that is associated with fractures. The last decade has seen a considerable increase in our knowledge of the epidemiology, mechanisms and therapeutic approaches to GIO. 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 GIO.

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Sažetak

GLUKOKORTIKOIDIMA IZAZVANA OSTEOPOROZA

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Liječenje glukokortikoidima je najčešći uzrok sekundarne osteoporoze i vodeći jatrogeni uzrok bolesti. Učestala manifestacija je prijelom koji se javlja u 30% do 50% bolesnika koji su uzimali dugotrajnu glukokortikoidnu terapiju. Glukokortikoidima izazvana osteoporoza uglavnom utječe na trabekularnu kost, kao što je lumbalna kralježnica i proksimalni dio bedrene kosti. Ostvaren je napredak u razjašnjavanju patofizioloških mehanizama koji rezultiraju glukokortikoidima izazvanom osteoporozom. Iako su mogućnosti za prevenciju i liječenje glukokortikoidima izazvane osteoporoze sve veće, dosadašnje preventivne mjere kao i liječenje su nedostatni.

Ključne riječi: *Glukokortikoidi; Liječenje; Sekundarna osteoporoza*