Corticosteroid-induced osteoporosis: Pathogenesis and prevention

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ABSTRACT

In spite of their adverse side effects, natural and synthetic glucocorticoids (GCs) occupy a unique role in several fields of medicine. They are potent regulators of bone cell growth and differentiation and the actions on the skeleton and related tissues depend on several factors including the dose, duration of the exposure, the steroid type and the species. In humans some of the effects are indirect, such as the regulation of intestinal calcium absorption and PTH secretion. Other effects are due to the cellular response that occurs within the bone microenvironment.

It has been well established in in vitro studies that GCs can promote osteoblast differentiation from mesenchymal osteoprogenitors both in rat calvarial culture and in adherent marrow stromal cells. Moreover, GCs are able to enhance expression of the mature osteoblast phenotype, increasing mineralized nodules, osteocalcin secretion, and the bone morphogenetic protein-6 message level. However, the mechanisms by which GCs affect bone metabolism are still unclear. Recent studies with GCs on bone cells suggested that the production of cytokines and growth factors and the expression of their receptors may also be influenced by GCs. In fact, GCs are able to inhibit the synthesis of cytokines, such as interleukin-1 which stimulates bone remodeling by monocytes and macrophages. Moreover, osteoprotegerin, a recently cloned member of the tumor necrosis factor receptor family, is downregulated by GCs, offering a possible interpretation for the induction of bone resorption by GCs.

GC-induced inhibition of bone resorbing cytokines may contribute to explain the therapeutic actions of GCs in several diseases such as rheumatoid arthritis and myeloma. Furthermore, GCs modulate osteoclast recruitment, even if there is no clear explanation for a direct effect of GCs on osteoclastic precursors. Sustained stimulation of matrix degradation by isolated avian osteoclasts incubated with GCs has been reported, as well as cytotoxic effects on osteoclastic cells from neonatal rat long bones.

Introduction

Glucocorticoid (GC)-induced osteoporosis has been recognized since 1932, when Cushing referred an "increased tendency to fracture" in a patient affecting by adrenal hyperplasia secondary to pituitary tumors producing adrenocorticotrophic hormone (1). Subsequently, when cortisone began to be used as therapeutic agent, it soon was clear that despite its beneficial anti-inflammatory and immunosuppressive effects, long-term treatment with high doses led to severe bone loss and several case reports of vertebral fractures were observed (2), indicating that exogenous hypercortisolism was also deleterious to the skeleton.

With the more restrictive use of GCs, severe adverse events as well as cushingoid appearance, secondary adrenal insufficiency and vertebral fractures have become rarer, but about 40-50% of patients requiring GC therapy develop osteoporosis. Researchers have reported GC-induced osteoporosis in patients on long-term, high dose GC therapy, and have also demonstrated a reduced bone mass due to an increase in bone resorption and a decrease in bone formation. The increased bone resorption is probably secondary to the enhanced production of parathyroid hormone, while the inhibited bone formation seems to be secondary to a decrease in collagen synthesis.

Despite these adverse side effects, natural and synthetic GCs occupy an unique role in several fields of medicine. Thus, it is of fundamental importance to individuate the specific effect of GCs on bone tissue and to adopt prophylactic and therapeutic measures against excessive bone loss.

Pathogenesis of glucocorticoid-induced osteoporosis

Osteoporosis is a syndrome characterized by a low rate of bone mass, microarchitectural deterioration of bone tissue leading to increased bone fragility and a consequent enhanced fracture risk. The main clinical manifestations are bone pain, pathological fractures in the axial and appendicular skeleton and skeletal deformities. In healthy persons a normal decline of bone mass (about 1-2% per year) is observed until the age of 25-35 years and may increase several fold in premenopausal women. Osteoporosis is a multifactorial syndrome and many risk factors have been established, including age, sex, race, and ovariectomy, prolonged immobilization and continued use of GCs.

The most rapid rate of GC-induced bone loss occurs in the first year of treatment (3) followed by a slower but continuing decline in bone mineral density (4), its degree depending on the duration of therapy and the dose used (5). Biopsies from patients affected by GC-induced osteoporosis showed a reduction in bone matrix apposition rates, decreased trabecular volume and enhanced bone resorption (6, 7).

The pathogenesis of GC-induced osteoporosis remain incompletely understood: and the best means for its treatment and/or prevention are still being debated. The decrease of bone formation is the major event in GC excess and results in a decrease in the serum level of osteocalcin, the specific marker of bone formation. In fact, GCs directly act on osteoblast (OB) cells, reducing OB recruitment (8) and activity as shown by the reduction in bone GLA protein osteocalcin and type I collagen. But GCs can also act through the modulation of OB growth factors and/or their receptors; insulin-like growth factor (IGF) is an important stimulator of OB activity and bone cells express IGF-I and IGF-II receptors. An increase of IGF-I receptors in OB has been reported, but the data are controversial, while IGF-II receptor expression is inhibited by GCs via transcriptional mechanisms (9). Moreover, the activity of IGFs is modulated by six IGF binding proteins (IGFBPs) that are expressed by OB and are considered important factors for the storage and transport of IGFs. GCs are able to decrease the expression of IGFBP-3, -4 and -5. In particular, the effect of IGFBP-5, which stimulates OB cell growth and enhances the effect of IGF-I, may be directly related to the inhibitory action of GCs on bone formation.

Transforming growth factor (TGF) β is a growth regulator of skeletal cells expressed in OB and osteoclast cells, that stimulates collagen synthesis and matrix apposition rates. It is released in the extracellular matrix in a biologically latent form that may be activated by several agents. GCs induce the activation of the latent form and through the suppression of CBFa1, transcription factor of the TGF β type I receptor with a resultant decrease in the expression and activity of the TGF β type I receptor on matrix-producing bone cells (10). Recently it has been reported that a new member of the tumor necrosis factor family, osteoprotegerin (OPG), is expressed in human OB-like cells and that the mRNA levels of this protein are inhibited by GCs, indicating that a reduced production of OPG from OB could in part explain GC-induced bone resorption (11). Indirect mechanisms probably are also involved, such as the inhibition of pituitary gonadotropin secretion and sex steroid production. Different effects of GCs on bone cell seem to depend on the stage of OB differentiation: in fact, corticosteroids induce the differentiation from preOB to OB, and stimulate the formation of bone nodules of mineralization; on the other hand they decrease the differentiated function of mature OB, decreasing cell duplication and suppressing type I collagen gene expression.

Prevention of glucocorticoid-induced osteoporosis

The prevention and treatment of GC-induced osteoporosis represent a real problem. Different treatment modalities have been proposed; for example, alternate-day therapy can minimize the adverse effects of GCs, resulting in partial or total restoration of bone mass. However, since discontinuous therapy is not feasible in many syndromes, the use of inhaled steroids and of GCs with bone-sparing properties has been proposed. Studies on the effect of inhaled steroids on bone are still limited and it is often difficult to assess their value because patients had frequently also received oral GC therapy. However, it has been demonstrated that inhaled steroids are absorbed because they are able to inhibit markers of differentiated OB, and to decrease bone mineral density with a dose dependent effect (12).

In order to maintain the clinical efficiency of the drugs while decreasing the known adverse effects, new GC molecules have been proposed. Deflazacort, an oxazoline derivative of prednisone, is a synthetic GC with antiinflammatory and antiimmune properties and it has been claimed to have a less inhibitory effect on bone as well as on glucose metabolism *in vivo.* However, *in vitro* studies have demonstrated that deflazacort and cortisol show comparable effects on inhibiting bone DNA and collagen synthesis (13). Most attempts to control bone loss associated with GCs have looked at improving calcium retention by increasing calcium absorption and decreasing urinary excretion. Vitamin D and its metabolites, calcium supplementation and thiazide diuretics have been used. 25-hydroxyvitamin D (calcifedol) or 1,25-dihydroxyvitamin D3 (calcitriol) can be administered to increase calcium absorption. One necessary precaution is the monitoring of treated patients for the possible development of hypercalcemia, which occurs in about 25% of patients taking GCs and receiving calcitriol at 0.6 µg daily and calcium supplementation (14).

Anti-resorptive drugs have also been employed in the treatment of GC-induced osteoporosis with the aim of preventing bone loss. Bisphosphonates, such as etidronate have been effective in preventing bone mineral loss observed in the spine and femur of postmenopausal women receiving GC therapy (15). But up-to-date information about the effectiveness of etidronate on fracture prevention in GC-induced osteoporosis is lacking. Moreover, it is still unclear if alendronate, which increases bone mineral density in postmenopausal osteoporosis, has any effect in GC-induced osteoporosis. Finally, since patients exposed to GCs have suppressed gonadotropin secretion,

sex steroid therapy has been proposed, but its efficacy has been demonstrated only in a small number of patients.

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