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Glucocorticoid-induced osteoporosis: 2013 update

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SUMMARY

Glucocorticoids are the most common cause of secondary osteoporosis leading to the so-called glucocorticoid-induced osteoporosis (GIO). A treatment with 10 mg/d of prednisone or equivalent for more than 3 months leads to a 7-fold increase in hip fractures and a 17-fold increase in vertebral fractures. The difference between bone quantity and quality in GIO makes bone mineral density measurements inadequate to detect patients at risk of fracture. The adverse effects of glucocorticoids on the skeleton derive from a direct impact on bone cells with a severe impairment of mechanical competence. Crucial to prevention of GIO is early timing of intervention. The World Health Organization has adopted a fracture prevention algorithm (FRAX) intended to estimate fracture risk in GIO. The American College of Rhematology modified its prevention and treatment guidelines taking into account the individual risk of fracture calculated in GIO on the basis of the FRAX algorithm. Recently, also a joint Guideline Working Group of the International Osteoporosis Foundation (IOF) and the European Calcified Tissue Society (ECTS) published a framework for the development of national guidelines for the management of GIO. Bisphosphonates are the first-line drugs to treat GIO; teriparatide counteracts several fundamental pathophysiologic aspects of GIO; denosumab is useful in patients with renal failure and in potentially pregnant young women. Vertebroplasty and kyphoplasty may be less beneficial in GIO than in primary involutional osteoporosis.

Key words: *Glucocorticoid-induced osteoporosis.*

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EPIDEMIOLOGY

Glucocorticoids (GCs) are very frequently used in the long-term treatment of patients with chronic diseases, such as rheumatoid arthritis, polymyalgia rheumatica, connective tissue diseases, inflammatory bowel disease, and chronic obstructive pulmonary disease.

A retrospective study showed that more than 80% of 365 rheumatoid patients followed for at least 10 years continuously in a single center (mean follow up 14.2±4.0 years) have taken GCs with a mean duration of exposure of 8 years (1). It has also been estimated that about 3% of the population aged 50 years or older has used GCs. This percentage climbs to 5.2% among over 80s or older patients (2).

Long-term glucocorticoid treatment, even at low doses (≤7.5 mg of prednisolone or equivalent), rapidly induces bone loss and increased risk of vertebral and non-vertebral fractures (3). Bone loss is more marked in the trabecular bone and starts soon after the initiation of therapy (3, 4) with a steep increase in vertebral and ribs fractures. The GC-induced bone loss unfolds over 2 phases: a rapid initial phase with a 3-5% loss in the first year of GC treatment and a subsequent slower phase with continued use and a 0.5-1% loss annually (5, 6).

Furthermore, GC use increases the risk of all fractures in a dose-dependent manner (7, 8) and is associated with a particularly high risk of vertebral fractures (2-5 times, depending on the daily dosage of prednisone).

The increase in fractures already occurs 3 months after treatment has started (9). In GC-induced osteoporosis there is a weak correlation between bone density (BMD) and fracture risk.

Besides bone loss, the risk of fracture is also increased by a reduced bone quality (10).

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PATHOGENESIS

The pathogenesis of GC-induced osteoporosis (GIO) is complex and involves both skeletal and extra-skeletal events. Earlier views on its pathogenesis stressed the extra-skeletal effects of GCs, such as a decrease in intestinal calcium absorption and an increase in renal calcium excretion (11-14). Calcium absorption from the gastrointestinal tract is inhibited by mechanisms that counter the action of vitamin D (15). It is also known that not only does prednisone increase the catabolism of 25(OH) D (16-18), but it may induce a significant weight gain.

On the long-term, this may compound the negative effects of GCs on vitamin D, which is soluble in fat and becomes less bioavailable (15, 19). As a consequence, secondary hyperparathyroidism may develop, even though several studies found normal parathyroid hormone levels in patients who follow a long-term GC treatment. Furthermore bone histomorphometric features indicate that secondary hyperparathyroidism does not play a key role in the pathogenesis of the bone disorders observed in GIO (12, 20). Exogenous GCs also decrease the secretion of adrenal androgens and estrogens (21), which is associated with changes in the growth hormone-insulin-like growth factor 1 (GH–IGF1) axis and insulin production (22, 23).

GH secretion is blunted by GCs (24, 25) mainly by an increased hypothalamic somatostatin tone. GCs also decrease IGF-I transcription in osteoblasts (26). Although hypogonadism, reduced production of IGF-I and increased losses of calcium from the kidney and intestine significantly contribute to GIO, the main sources of skeletal damage during a GC treatment are considered to be the direct effects on all cell types (11, 12, 14, 27).

At the cellular level, the most marked effect of GCs is a decrease in osteoblastogenesis due to inhibition of the Wnt β-catenin signaling pathway and an increase in osteoblast apoptosis due to the activation of caspase 3 (28, 29), resulting in decreased bone formation (11, 12, 14). The impairment of the osteoblast differentiation of the bone marrow stromal cells is accompanied by a shift towards the adipocytic lineage due to a decrease in bone morphogenetic protein-2 and a repression of runt related protein 2 (Runx2) associated with an increase in peroxisome proliferator-activated receptor γ2 (PPARγ2) and in CAAT enhancer-binding proteins (12, 14, 30, 31).

The inhibition of the Wnt β-catenin pathway has emerged as a key mechanism underlying reduced bone formation (32, 33). In bone metabolism, the Wnt signal plays a pivotal role in osteoblastogenesis (34). This pathway is negatively regulated by dickkopf-1 (Dkk-1) and sclerostin. GCs lead to an upregulated expression of these inhibitors (35-27), thereby suppressing the binding of Wnt to low-density lipoprotein receptor–related proteins 5 and 6 (LPR5/-6). This leads to a reduced ability to stabilize β-catenin and to the inhibition of bone formation by blocking the transcription of target genes (38).

Emerging data also suggest an additional pathogenic event in the significant decrease of bone formation associated with GCs. Decreased osteoblastogenesis might also be due to the attenuation of the serine/threonine kinase Akt activity and Forkhead box O (FoxO)-mediated inhibition of Wnt signaling, as well as increased osteoblast apoptosis, which might also result from an increase in reactive oxygen species (ROS) and activation of the ROS/ PKC_/p66shc/ JNK cascade (39-41).

In animal and *in vitro* studies GCs increased ROS and the phosphorylation of p66shc (an amplifier of H2O2 generation in mitochondria) in osteoblasts (39). Consequently the generation of ROS via PKC_/p66shc signaling converts oxidative signals into apoptosis of osteoblasts (39, 40). The increase of ROS is also responsible for the activation of FoxO transcription factors expressed in bone cells, which play a critical role in bone homeostasis (40).

As a result of the suppressed Akt activity by GCs (39), ROS promote FoxO binding to β-catenin and thereby divert β-catenin from TCF- to FoxO-mediated transcription causing a decrease in osteoblastogen-

esis (39-41). The activation of caspase 3, a common downstream effector of several apoptotic signaling pathways (28, 29) in response to GCs also results in increased apoptosis of osteocytes (12, 14, 27, 42). Osteocytes function as mechanosensors and their interlacing dendrites form a network of channels transmitting information to the bone surface (42, 43).

The loss of osteocytes might be particularly important for the bone structure, because this mechanosensor is important in the repair of bone microdamage (42, 43). Disruption of the osteocyte–canalicular network, because of osteocyte apoptosis, results in a failure to detect signals that normally stimulate the replacement of the damaged bone (44) and could adversely affect the material properties of the surrounding bone, independently of changes in bone remodeling or architecture.

Additionally, the increased osteocyte apoptosis is associated with a decrease in vascular endothelial growth factor and skeletal angiogenesis (45). Therefore the effect of GCs on osteocytes might account for a disproportionate loss of bone strength in relation to the bone mass.

In contrast to osteoblastogenesis, osteoclastogenesis is actually promoted by the use of GCs, which increase the expression of M-CSF and RANK-L, and decrease the expression of its soluble decoy receptor, osteoprotegerin, in stromal and osteoblastic cells (14, 46, 47). GCs also enhance the expression of interleukin-6, an osteoclastogenic cytokine, and suppress the expression of interferon-β, an inhibitor of osteoclastogenesis (48, 49). In accordance with their effects on bone resorption, GCs enhance the expression of selected matrix metalloproteinases (MMP).

Osteoblasts secrete MMP1 or collagenase 1 and MMP13 or collagenase 3, and both cleave type I collagen fibrils at a neutral pH (50, 51). Cortisol increases the synthesis of collagenase 3 by post-transcriptional mechanisms, regulating specific cytosolic RNA binding proteins, and their binding to specific RNA sequences (52).

One of the most typical features of GIO is the large inter-individual variability in its clinical presentation and severity, the cause of which is yet to be fully understood in both in exogenous and endogenous hypercortisolism. Individual susceptibility to GCs varies considerably and may be explained by differences in the absorption, distribution or metabolism of the steroid molecule, or in the number and affinity of GC receptors or their nuclear cofactors (53, 54). Clinical and *in vitro* studies propose a potential role of polymorphisms of the GC receptor gene not only as cause for GC sensitivity in patients with inflammatory disorders (14, 54), but also as a regulator of differences in BMD and body composition (55).

An attractive explanation to account for differences in skeletal susceptibility to GCs has been identified in the past decade and is related to a peripheral enzyme system of 11β-hydroxysteroid dehydrogenases (11β-HSD), which regulates the interconversion of the inactive hormone (cortisone) into the active hormone (cortisol) (53).

Therefore, this enzyme system plays a crucial role in the regulation of GC activity (56). Two distinct enzymes have been described in humans: type 1 and type 2 11β-hydroxysteroid dehydrogenase (11β-HSD).

Type 2 11β-HSD is expressed in tissues with high concentrations of GC receptors, such as the liver and the adipose tissue, and acts as an inactivating enzyme by converting cortisol into cortisone (56). By contrast, type 1 11β-HSD is primarily a GC activator, converting cortisone into cortisol.

Type 1 11β-HSD type 1 also favors the synthesis of active GCs in osteoblasts, affecting their proliferation and differentiation, and is widely expressed in target tissues of GC action (56).

The activity of type 1 11β-HSD and therefore its ability to generate cortisol from cortisone in human osteoblasts is stimulated by proinflammatory cytokines and exogenous GCs themselves (57).

An increase in the activity of type 1 11β-HSD is also enhanced by aging, providing a pathogenic explanation for the markedly enhanced GC effects in the skeleton of elderly subjects (56).

MANAGEMENT OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS

When a patient starts a GC treatment which is intended to last at least 3 months, adequate prevention measures against fractures need to be adopted. The same applies to patients already on GCs. Several clinical trials have assessed the effect of bisphosphonates and teriparatide on BMD and fracture risk in patients on GC therapy. Alendronate and risedronate, two biphosponates, have shown to increase BMD and reduce vertebral fracture risk in GC receivers (58-61). Ibandonate, another bisphosphonate, given once monthly, has increased BMD (62).

The zoledronic acid, a bisphosphonate administered in a single annual dose, has shown to increase BMD more than oral risedronate taken daily (63). Lastly teriparatide, the active 1-34 site of the parathyroid hormone, has proven superior to alendronate (64). However, despite the well-known risk of fractures with GC use and the demonstrated efficacy of these agents in preventing bone loss and fracture, many patients do not receive any such treatment (65, 66).

Various guidelines for GIO stress the importance of initiating an anti-osteoporosis prophylaxis in patients receiving long-term GC therapy (67, 68).

The first step in the prevention process is to encourage all patients receiving GCs to modify their lifestyle, although the evidence of effects of this strategy on fracture risk is weak. In any case adequate levels of dietary calcium intake, adequate exercise, good nutrition, and maintenance of a normal body weight should be encouraged, whereas smoking and alcohol abuse should be avoided. Also an assessment of the risk of falls is recommended and should be accompanied by advice on how to reduce it. Furthermore, the dose of GCs should be periodically reviewed and kept to a minimum. Alternative routes of administration (*e.g.* topical, inhaled) or formulations (*e.g.* budesonide) may be considered, and in some situations, the use of alternative immunosuppressive agents may enable reduction in the dose of GCs. There is an almost universal agreement that daily calcium intake (supplement plus oral intake) should be in the order of 1200-1500 mg, and that vitamin D supplementation should be sufficient to achieve therapeutic levels of 25-hydroxyvitamin D or dosage of 800-1000 IU/day (67, 68).

Ideally, the timing of the pharmacological anti-osteoporotic intervention in GIO should be based on the individual absolute risk of fracture. The World Health Organization (WHO) developed the FRAX® computer-based fracture risk-assessment tool (http://www.shef.ac.uk/FRAX) to calculate a 10-year fracture probability starting from clinical risk factors with or without BMD testing (69, 70).

This risk-assessment tool provides estimates of fracture probability in individuals receiving GC doses of 2.5-7.5 mg/day, whereas the underlying algorithm can be adjusted according to the GC dose defined in terms of prednisolone-equivalent doses (71). For a low-dose exposure (<2.5 mg/day prednisolone equivalent) the probability of a major fracture may be downsized, depending on age, whereas with high doses (≥7.5 mg/day) the probabilities fractures can be increased (71).

Thresholds for cost-effectiveness have been developed on the basis of economic assumptions that are country-specific. In the United States, the National Osteoporosis Foundation recommends a drug therapy if the 10-year absolute risk of a major osteoporotic fracture of the hip, spine (clinical, not radiographic), wrist, or humerus is greater than 20% or if the risk of hip fracture is greater than 3% (72).

Various guidelines for GIO stress the importance of initiating an anti-osteoporosis prophylaxis in patients receiving chronic GC therapy (67, 68). The most recent (2010) recommendations from the American College of Rheumatology (ACR) are stratified by GC dose and fracture risk based on FRAX calculations. For postmenopausal women and men aged 50 and older, they recommend that low- and medium-risk patients (FRAX 10-year risk of a major fracture <10 and 10–20 %, respec-

tively) should be treated if their GC dose is ≥7.5 mg/day and GC use is expected to last or has already lasted at least 3 months. Medium-risk patients (FRAX 10–20%) should be treated even if their GC daily dose is <7.5 mg. High-risk patients (FRAX >20%) should be treated for any duration and dose of GCs (67).

For premenopausal women and men younger than 50, the decision is based on previous fractures. For patients who have not had previous fractures, data was considered too limited to issue a recommendation, whereas in premenopausal women with no childbearing potential who have had a fracture, treatment is indicated if the patient has received GCs at any dose for longer than 3 months, or if the GC dose is ≥7.5 mg/day for 1 to 3 months, or even if the dose is ≥5 mg/day, even though in this case only alendronate or risedronate are recommended.

Lastly, in premenopausal women with childbearing potential who have had a fracture, there are further complexities to consider, given the potential fetal toxicity of bisphosphonates. In short-term GC therapy at any dose and for a therapy >3 months at less than 7.5 mg/day, no consensus has yet been reached by the ACR panel of experts about whether to initiate treatment or not. For therapies lasting >3-month at a dose of ≥7.5 mg/day, treatment is recommended, avoiding the use of zoledronate based on the long half-life of the drug and concern for fetal toxicity (67).

A joint Guideline Working Group of the International Osteoporosis Foundation (IOF) and the European Calcified Tissue Society (ECTS) has recently published a framework for the development of national guidelines for the management of GIO (68). The IOF–ECTS recommends that, in postmenopausal women and men aged ≥50 years exposed to ≥3 months of oral GCs, a decision should be made on whether to consider treatment directly or to assess risk with adjusted FRAX (with or without BMD testing). This decision should be based on the history of the fracture, age (≥70 years), and GC dose (≥7.5 mg/day). Intervention thresholds based on FRAX will also depend on the country. In premenopausal women and men aged <50 years exposed to ≥3 months of oral GC, treatment should be considered in patients with prior fracture. Treatment decisions in individuals with no prior fracture should be based on clinical judgment. In addition, it is recommended that all individuals receiving GC therapy should be counseled as to the risks of treatment.

General measures (e.g., good nutrition and regular weight-bearing exercise) should be taken, and patients should be monitored as appropriate (Tab. I) (68).

Bisphosphonates are considered first-line options for GIO (73). Randomized, placebo-controlled trials have shown that alendronate, risedronate, and zoledronic acid are effective for this indication and reduce the risk of vertebral but not hip fractures (60, 63, 74).

More recently, once-monthly oral ibandronate offered significant improvement in bone mineral density in postmenopausal women treated with GCs for inflammatory rheumatic disease in a 12 month, randomized, double-blind, placebo-controlled trial (62). The evidence for bisphospho-

Table I - General measures and recommendations in the management of glucocorticoid-induced osteoporosis.

General measures
• Glucocorticoid-sparing therapy: reduce glucocorticoid dose whenever possible
• Consider alternative route of glucocorticoid administration
• Recommend good nutritional habits, especially in relation to calcium and vitamin D
• Recommend regular weight-bearing exercise
• Avoid tobacco use and alcohol abuse
• Assess fall risk and advise accordingly
Monitoring recommendations during glucocorticoid therapy
• Assess compliance to therapy, including use of calcium and vitamin D
• If a vertebral fracture is suspected, assess by X-ray or DXA
• Measure height annually and BMD at appropriate intervals (especially in patients on high glucocorticoid doses)
• Measure serum P1NP after 3 months from the beginning of teriparatide therapy

DXA, dual x-ray absorptiometry; BMD, body mass density.

nate treatment in GIO is not as strong as in postmenopausal osteoporosis, because the primary end point in the GC treatment trials was BMD rather than fracture, and - as explained by the current knowledge in the field of pathophysiology - GCs increase fracture incidence in a way that is partly independent of BMD. In addition, most studies have only lasted 12-18 months and were conducted on insufficient numbers of patients to be able to identify any difference in the incidence of hip fractures.

An advantage of oral bisphosphonates is that they can be stopped, if GCs are discontinued, but compliance with oral formulations is poor.

Annual infusions of zoledronic acid can certainly solve the compliance problem and provide rapid skeletal protection, if GC therapy has already lasted >90 days. In this case, there may not be time to wait for the delayed protective effects of oral bisphosphonates, because of their very low oral absorption and lower potency compared with zoledronic acid. Since a substantial BMD loss occurs in patients who discontinue bisphosphonates, while receiving GCs, it is recommended to continue the bisphosphonate treatment as long as the GC treatment lasts.

All bisphosphonates used for the treatment of GIO require caution, if the patient could potentially be pregnant, due to its long half-life. This is particularly true for the zoledronic acid (67).

An alternative GIO treatment is teriparatide, a recombinant human parathyroid hormone (1-34). In an 18-month randomized, double-blind, placebo-controlled trial, teriparatide increased spinal BMD faster and to a greater extent than alendronate and also reduced vertebral fractures (75).

Teriparatide represents a particularly rational approach to GIO, because it counters some fundamental aspects of its pathophysiology, such as the expected GC-induced increase in osteoblast and osteocyte apoptosis and the decrease in the number of osteoblasts. The decreased osteoblast apoptosis leads to an increase in bone formation, while the decreased osteocyte apoptosis is associated with a preservation of bone strength (76). Another potential treatment option is denosumab, a humanized monoclonal antibody to RANKL approved for the prevention of vertebral, nonvertebral, and hip fractures in women with postmenopausal osteoporosis, but not yet for GIO. In a randomized, double-blind, placebo-controlled trial of denosumab in patients with rheumatoid arthritis receiving less than 15 mg/day of prednisone and methotrexate or methotrexate alone, denosumab reported similar effects in both groups in terms of BMD of the spine and the hip (77). Denosumab may be considered for GC-treated patients with renal failure who are not candidates for bisphosphonates or teriparatide. The ease of administration via subcutaneous injections every 6 months may increase compliance. In patients with GIO, if pain deriving from fractured vertebrae is significant, persistent and resistant to conventional therapy, vertebroplasty and kyphoplasty may be indicated. However, increased fractures in the adjacent vertebrae have been reported, suggesting that prudence should be used before recommending this kind of procedure in these patients (78).

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