

SUMMARY POINTS

- Bone-loss prevention should begin when glucocorticoid therapy begins.
- Glucocorticoids accelerate bone resorption, decrease bone formation, interfere with osteoblast maturation, decrease calcium resorption from the GI tract, and increase renal excretion of calcium.
- Glucocorticoid dose, duration of use, and initial bone mineral density are important risk factors.

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Glucocorticoid-Induced Osteoporosis: Prevention and Treatment

Peter Coutlakis, MD, and
 Lenore M. Buckley, MD MPH
 Virginia Commonwealth University,
 Medical College of Virginia, Richmond, VA

Introduction

Since glucocorticoids (GCs) were first employed in the treatment of rheumatoid arthritis by Hench et al. in 1949, their use has become widespread in the treatment of many inflammatory diseases such as asthma, arthritis, and other autoimmune diseases, as well as after organ transplantation. Treatment with GCs is complicated by many well-known potential toxicities. Although bone loss is initially asymptomatic, osteoporosis and fractures are the most common cause of serious long-term morbidity (1). New therapies for preventing and treating glucocorticoid-induced osteoporosis (GIOP) are available, but use of preventive treatments varies significantly by physician specialty (2). Recent studies have demonstrated that many patients receive no preventive treatment for bone loss while receiving GC treatment (3-5).

The goal of this article is to raise the awareness of GIOP, to describe the current understanding of pathogenesis and clinical course of the disease, and to update physicians on the management options for both primary prevention and treatment.

Epidemiology and Clinical Scope

The initial phase of GC treatment (3-6 months) is associated with rapid bone loss of as much as 10%-30% in trabecular bone. Subsequently, bone loss continues at a slower rate of

1%-2% per year (6,7). Accelerated bone loss may occur even in patients receiving low doses of GCs. Inhaled GCs are much safer, and although changes in markers of bone turnover have been reported with high doses of inhaled glucocorticoids, they do not appear to have a clinically important effect on bone density in most adults. Some improvements in bone mass can occur after withdrawal of GC treatment, but recovery is not complete (8,9). The amount of recovery varies with the age of the patient and the underlying bone mass. Recovery is less likely in the elderly and others with low bone turnover.

Loss is greatest in the trabecular bone of the spine and ribs, causing a threefold to fourfold increase in vertebral fracture rates. It also occurs, although more slowly, in the cortical bone of the femoral neck. Of women using long-term (at least a year or more) GCs, 28%-36% have vertebral fractures (10,11). Bone loss from GCs is related to dose and duration of treatment, as well as other risk factors such as hormonal status, genetics, and baseline bone mineral density (BMD). Although young people lose bone more rapidly, people with low bone mass at the time of GC treatment, such as postmenopausal women, are at greater risk of fracture (12,13).

Pathogenesis of GIOP

Glucocorticoids exert their effects on calcium homeostasis and bone metabolism through several mechanisms. Even low doses of GCs are associated with a decrease in gonadal hormones (estrogen and testosterone) that can accelerate bone resorption and decrease bone formation. Glucocorticoids interfere with osteoblast maturation and accelerate apoptosis, resulting in decreased bone formation (14). They decrease calcium absorption from the gastrointestinal tract and increase renal excretion of calcium.

Some studies have found an increase in parathyroid hormone levels associated with GC therapy, which causes increased bone resorption and calcium excretion.

The associated steroid-induced myopathy seen in some patients may also play a role in bone loss by altering forces important in bone remodeling. Glucocorticoids also appear to inhibit several important growth factors and cytokines such as insulin-like growth factor 1 (IGF-1), transforming growth factor beta (TGF- β), and osteoprotegerin (15).

Prevention and Treatment of GIOP

Primary prevention – starting bone-preserving therapy at the initiation of GC treatment before bone loss begins – is of paramount importance. Bone resorption occurs in the first 3-6 months, and treatments are now available to prevent it. In addition, the lowest effective dose of GCs should be used and the dose should be decreased as rapidly as possible given the underlying disease. Topical and inhaled steroids are preferred when possible. Treatment strategies should include an exercise program.

Patient Evaluation and Risk Assessment

Guidelines for measuring BMD in GIOP have been developed by the National Osteoporosis Foundation, the American College of Rheumatology (ACR), and others (16-19). Most recommend a baseline BMD study, usually a dual-energy x-ray absorptiometry (DEXA) scan, at the start of therapy in patients receiving 7.5 mg/day or more of prednisone who will be treated for at least 3-6 months. Baseline BMD is an essential part of the risk stratification used in determining therapy. Recommendations concerning follow-up BMD studies to determine efficacy of preventative therapy vary from 6 months to 2 years. Most insurers will cover yearly BMD assessments (17).

Calcium and Vitamin D Supplementation

Calcium and vitamin D3 play an important role in preventing bone loss in patients receiving low-dose GCs. The

effects of calcium and vitamin D have been demonstrated in patients receiving low-dose and high-dose treatment, and in patients on long-term treatment (7) as well as those initiating treatment (13). In a meta-analysis, Amin and colleagues (20) demonstrated that calcium and vitamin D supplements decreased bone loss similar to calcitonin. The ACR currently recommends calcium intake of at least 1,500 mg/day and vitamin D intake of 400-800 IU/day (16). Treatment with calcitriol (1,25-dihydroxyvitamin D3), a more potent form of vitamin D, has also been shown to prevent bone loss during high-dose GC treatment (21). However, it may cause hypercalcemia and hypercalciuria in up to 25% of patients and requires close monitoring. Calcitriol treatment may be more important for patients with renal disease (creatinine > 3.0) who are unable to metabolize vitamin D to its active metabolite and for people with other diseases that interfere with the absorption or metabolism of vitamin D, such as inflammatory bowel disease.

Although calcium and vitamin D supplementation are important agents in the prevention of GIOP, they will not eliminate all bone loss in all patients receiving moderate to high doses of GCs. They are inadequate treatment for patients with established osteoporosis. However, they should be included in all treatment regimens.

Bisphosphonates

Bisphosphonates are potent agents that inhibit bone resorption by osteoclasts. The first generation bisphosphonates etidronate and intravenous pamidronate have been shown to be effective in preventing GIOP in prospective randomized trials (22,23). Etidronate has a more modest effect on BMD (0.6% increase in the lumbar spine at 1 year) than newer agents such as alendronate, but it has the advantage of intermittent administration (400 mg daily for 2 weeks every 3 months). The risk of vertebral fracture with intermittent etidronate therapy decreased by 40%. Intermittent intravenous pamidronate (30 mg infused intravenously every 3 months) is an alternative for people who are unable to tolerate oral bisphosphonates.

The second and third generation bisphosphonates alendronate and risedronate are also effective in increasing BMD and decreasing vertebral fractures in GC users. Oral alendronate increased lumbar spine BMD 2.1% and 2.9%, respectively, for the 5-mg/day and 10-mg/day doses at 1 year (13). There was a 40% reduction in vertebral fracture rates at 1 year and 90% reduction at 2 years. The 5-mg daily dose of alendronate is recommended for prevention, and the 10-mg daily dose for treatment of patients with established osteoporosis and for postmenopausal women not receiving hormone replacement therapy (HRT). Recent studies have suggested that the total weekly dose of alendronate may be given once a week, perhaps with equivalent effects on bone density and no increase in toxicity (23). For some patients, weekly dosing with a 40-mg (prevention) or 70-mg (treatment) dose of alendronate may be more convenient. Risedronate has been approved by the Food and Drug Administration for the prevention of GIOP with effects similar to alendronate (24). The bisphosphonates are all superior to calcium and vitamin D alone in preventing and treating GIOP and should be considered when starting GC treatment in patients with osteopenia (t score less than -1 to -2.5) and osteoporosis (t score less than -2.5). Because they are renally excreted, bisphosphonates cannot be used in patients with significant renal insufficiency (creatinine \geq 3.0).

Calcitonin

Calcitonin has a direct inhibitory effect on osteoclasts and is considered a weak antiresorptive agent compared to bisphosphonates. It can be administered either subcutaneously or intranasally (200 IU/day in alternating nostrils). Although several studies demonstrated efficacy in preventing bone loss during GC therapy, others have shown that it has no additional benefit over adequate calcium and vitamin D supplementation (25-29). It has not been shown to prevent bone loss at the femoral neck. The advantages of calcitonin are that it has few side effects and may have analgesic properties in treating pain from

vertebral fractures (30). It may be most useful when preventing bone loss is the goal rather than significantly increasing it, for patients who cannot take bisphosphonates, and for temporary use for painful vertebral fractures.

Hormone Replacement Therapy

Glucocorticoids decrease estrogen levels in women and testosterone levels in men. The patients most likely to experience a vertebral fracture due to GC treatment are postmenopausal women because of their low initial bone mass. Hall and colleagues (31) reported that postmenopausal women receiving HRT have higher vertebral BMDs after treatment with low doses of glucocorticoids than women receiving calcium alone. There are no large controlled studies of the effects of estrogen on bone loss in postmenopausal women starting GC treatment. It remains unclear whether starting HRT and calcium with vitamin D is adequate therapy to prevent bone loss in, for example, an elderly woman starting moderate-dose GC for the treatment of polymyalgia rheumatica. As in the treatment of non-GIOP osteoporosis, the risks and benefits of HRT must be carefully weighed on an individual basis. Although selective estrogen receptor modulators (SERMs), like raloxifene, improve BMD at least in the spine in postmenopausal women, there are no studies of SERMs in patients receiving GC treatment. In addition, testosterone replacement increases BMD in hypogonadal men (32).

Future Therapies

The antiresorptive agents, while very effective in preventing and treating GIOP, do not lead to large increases in BMD in patients with severe osteoporosis. Treatments are needed that will increase bone formation by osteoblasts. Human parathyroid hormone (hPTH) is initially associated with an increase in bone formation, and a recent study demonstrated that hPTH increased vertebral BMD 10% in postmenopausal women taking GCs who are already on HRT and calcium (33). A corresponding decrease in fracture rates is likely but has not yet been shown.

An Approach to Management of GIOP

Patients taking more than 5-7.5 mg/day of prednisone or an equivalent dose of another GC for 3-6 months or more should receive preventive treatment. All patients should receive adequate calcium and vitamin D intake regardless of BMD or dose of GC. In addition, HRT should be considered for all postmenopausal women without contraindications; testosterone should be considered for hypogonadal men. Baseline BMD testing and a basic work-up should be done to rule out other causes of bone loss, such as medication (eg, phenytoin), significant renal disease, or significant gastrointestinal disease that might result in problems with vitamin D metabolism.

For patients with normal BMD (BMD t score of -1 or higher) receiving relatively low doses of GCs (<10 mg prednisone), calcium and vitamin D supplementation may be adequate prevention if the patient does not have other causes of bone loss such as menopause. Bone mineral density should be monitored periodically during GC treatment (every 1-2 years). Although cost-effectiveness studies are not available, most patients with osteopenia (BMD t score less than -1 to -2.5) treated with moderate to high doses (10 mg daily or more) of GCs should receive additional treatment to prevent bone loss. Lower-cost preventive treatments such as cyclic etidronate (400 mg daily for 2 weeks every 13 weeks) and low-dose alendronate (35-40 mg given once weekly) may be reasonable, improving compliance and tolerability. Calcitonin is more expensive but should be considered for patients who cannot take oral therapy, patients with renal insufficiency, or those who are intolerant of bisphosphonates.

For patients receiving GCs who are already osteoporotic (BMD t score less than -2.5), options include the 70-mg dose of alendronate (10 mg daily or 70 mg weekly), risedronate (10 mg daily), pamidronate (30 mg intravenously every 3 months) for those who cannot tolerate oral bisphosphonates, and HRT. For women with severe osteoporosis, the combination of a bisphosphonate (alendronate or risedronate) with HRT may be considered, although studies

to support this in GC-treated patients are not available. Monitoring bone density yearly during GC treatment can give further information about the effects of GC in an individual patient and the need for adjustments to treatment regimens.

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