CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will take steps to prevent and treat bone loss in their patients receiving long-term glucocorticoids

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How to prevent glucocorticoid-induced osteoporosis

ABSTRACT

When prescribing glucocorticoids for long-term treatment, physicians should take steps to prevent osteoporosis, a common and serious side effect of these drugs.

KEY POINTS

Glucocorticoids have both direct and indirect effects on bone cells, and they both suppress bone formation and promote resorption.

Patients who need glucocorticoids should receive the lowest effective dose for the shortest possible time. They should also be advised to undertake general health measures, including stopping smoking, reducing alcohol intake, exercising daily, and taking in adequate amounts of calcium and vitamin D.

Bisphosphonates and teriparatide (Forteo) are approved for treating glucocorticoid-induced osteoporosis, but adherence to guidelines for managing this condition is far from optimal.

Although glucocorticoid drugs such as prednisone, methylprednisolone, and dexamethasone have many benefits, they are the number-one cause of secondary osteoporosis.[1] When prescribing them for long-term therapy, physicians should take steps to prevent bone loss and fractures.

Being inexpensive and potent anti-inflammatory drugs, glucocorticoids are widely used to treat many diseases affecting millions of Americans, such as dermatologic conditions, inflammatory bowel disease, pulmonary diseases (eg, asthma, chronic obstructive pulmonary disease, interstitial lung disease), renal diseases (eg, glomerulonephritis), rheumatologic disorders (eg, rheumatoid arthritis, lupus, vasculitis, polymyalgia rheumatica), and transplant rejection.

This article discusses the mechanisms of glucocorticoid-induced bone loss and guidelines for preventing and treating it.

GLUCOCORTICOIDS PROMOTE BONE LOSS DIRECTLY AND INDIRECTLY

The pathophysiology of glucocorticoid-induced osteoporosis is much more complicated than was previously thought.

The older view was that these drugs mostly affect bone indirectly by inhibiting calcium absorption, causing secondary hyperparathyroidism. Indeed, they do inhibit calcium absorption from the gastrointestinal tract and induce renal calcium loss. However, most patients do not have elevated levels of parathyroid hormone.

Now, reduced bone formation rather than increased bone resorption is thought to be the predominant effect of glucocorticoids on bone

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turnover, as these drugs suppress the number and the activity of osteoblasts.

Direct effects on bone

Glucocorticoids directly affect bone cells in a number of ways—eg, by stimulating osteoclastogenesis, decreasing osteoblast function and life span, increasing osteoblast apoptosis, and impairing preosteoblast formation.[2]

Glucocorticoids also increase osteocyte apoptosis.[3] Osteocytes, the most numerous bone cells, are thought to be an integral part of the "nervous system" of bone, directing bone-remodeling units to locations where repair of bone microfractures or removal of bone is needed. Osteocyte apoptosis caused by glucocorticoids may disrupt the signaling process, resulting in increased osteoclast activity in an area of apoptotic osteocytes and the inability to directly repair bone, thus impairing the bone's ability to preserve its strength and architecture. Such disruption may affect bone quality and increase the risk of fracture independent of any decrease in bone mineral density.[4]

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Direct molecular effects

Glucocorticoids have been found to:

- Block the stimulatory effect of insulin-like growth factor 1 on bone formation[5]
- Oppose Wnt/beta-catenin signaling, resulting in decreased bone formation[6]
- Affect stromal cell differentiation, shunting cell formation towards more adipocyte formation so that fewer osteoblasts and chondrocytes are formed, resulting in less bone formation
- Increase levels of receptor activator of nuclear factor kappa (RANK) ligand and macrophage colony-stimulating factor and decrease levels of osteoprotegerin, resulting in increased osteoclastogenesis and increased bone resorption[7]
- Decrease estrogen, testosterone, and adrenal androgen levels, which also have adverse effects on bone cells.[8]

Inflammatory diseases also affect bone

Furthermore, many patients taking glucocorticoids are already at risk of osteoporosis because many of the diseases that require these drugs for treatment are associated with bone loss due to their inflammatory nature. In rheumatoid arthritis, RANK ligand, one of the cytokines involved in inflammation, causes bony erosions and also causes localized osteopenia. The malabsorption of calcium and vitamin D in inflammatory bowel disease is a cause of secondary osteoporosis.

Trabecular bone is affected first

The degree of bone loss in patients receiving glucocorticoids can vary markedly, depending on the skeletal site. Initially, these drugs affect trabecular bone because of its higher metabolic activity, but with prolonged use cortical bone is also affected.[2] Greater trabecular thinning is seen in glucocorticoid-induced osteoporosis than in postmenopausal osteoporosis, in which more trabecular perforations are seen.[9]

Bone loss occurs rapidly during the first few months of glucocorticoid therapy, followed by a slower but continued loss with ongoing use.

FRACTURE RISK INCREASES RAPIDLY

With this decrease in bone mass comes a rapid increase in fracture risk, which correlates with the dose of glucocorticoids and the duration of use.[10] Vertebral fractures resulting from prolonged cortisone use were first described in 1954.[11]

A dosage of 5 mg or more of prednisolone or its equivalent per day decreases bone mineral density and rapidly increases the risk of fracture over 3 to 6 months. The relative risks[12]:

- Any fracture—1.33 to 1.91
- Hip fracture—1.61 to 2.01
- Vertebral fracture—2.60 to 2.86
- Forearm fracture—1.09 to 1.13.

These risks are independent of age, sex, and underlying disease.[12]

Patients receiving glucocorticoids may suffer vertebral and hip fractures at higher bone mineral density values than patients with postmenopausal osteoporosis. In 2003, van Staa et al[13] reported that, at any given bone mineral density, the incidence of new vertebral fracture in postmenopausal women receiving glucocorticoids was higher than in nonusers. This suggests that glucocorticoids have both a qualitative and a quantitative effect on bone.

Glucocorticoids also cause a form of myopathy, which increases the propensity to fall, further increasing the risk of fractures.

Fracture risk declines after oral glucocorticoids are stopped, reaching a relative risk of 1 approximately 2 years later.[12] However, keep in mind that the underlying conditions being treated by the glucocorticoids also increase the patient's fracture risk. Therefore, the patient's risk of fracture needs to be evaluated even after stopping the glucocorticoid.

INHALED STEROIDS IN HIGH DOSES MAY ALSO INCREASE RISK

Although inhaled glucocorticoids are generally believed not to affect bone, some evidence suggests that in high doses (> 2,000 µg/day) they may result in significant osteoporosis over several years.[14,15]

In a retrospective cohort study, van Staa et al[15] compared the risk of fracture in 171,000 patients taking the inhaled glucocorticoids fluticasone (Flovent), budesonide (Pulmicort), or beclomethasone (Beconase); 109,000 patients taking inhaled nonglucocorticoid bronchodilators; and 171,000 controls not using inhalers. They found no differences between the inhaled glucocorticoid and nonglucocorticoid bronchodilator groups in the risk of nonvertebral fracture. Users of inhaled glucocorticoids had a higher risk of fracture, particularly of the hip and spine, than did controls, but this may have been related more to the severity of the underlying respiratory disease than to the inhaled glucocorticoids.

Weldon et al[16] suggested preventive measures to prevent glucocorticoid-induced effects on bone metabolism when prescribing inhaled glucocorticoids to children. They stated that prophylaxis against osteoporosis requires suspicion, assessment of bone density, supplemental calcium and vitamin D, and, if indicated, bisphosphonates to prevent bone fractures that could compromise the patient's quality of life.

PREVENTING AND TREATING BONE LOSS DUE TO GLUCOCORTICOIDS

Effective options are available to prevent the deleterious effects of glucocorticoids on bone.

A plethora of guidelines offer direction on how to reduce fracture risk—ie, how to maintain bone mineral density while preventing additional bone loss, alleviating pain associated with existing fractures, maintaining and increasing muscle strength, and initiating lifestyle changes as needed.[17,18] Guidelines from the American College of Rheumatology (ACR),[17] published in 2001, are being updated. United Kingdom (UK) guidelines,[18] published in December 2002, differ slightly from those of the ACR.

Limit exposure to glucocorticoids

Oral glucocorticoids should be given in the lowest effective dose for the shortest possible time. However, there is no safe oral glucocorticoid dose with respect to bone. Alternate-day dosing suppresses the adrenal axis less but has the same effect as daily dosing with regard to bone.

Recommend lifestyle measures from day 1

All guidelines recommend that as soon as a patient is prescribed a glucocorticoid, the clinician should prescribe certain preventive measures, including:

- Smoking cessation
- Weight-bearing and strength-building exercises
- Calcium intake of 1,000 to 1,500 mg per day
- Vitamin D 800 to 1,000 IU per day.

Calcium and vitamin D for all

The Cochrane Database of Systematic Reviews[19] evaluated the data supporting the recommendation to use calcium and vitamin D as preventive therapy in patients receiving glucocorticoids. Five trials with 274 patients were included in the meta-analysis. At 2 years after starting calcium and vitamin D, there was a significant weighted mean difference of 2.6% (95% confidence interval [CI] 0.7–4.5) between the treatment and control groups in lumbar spine bone mineral density.

The authors concluded that because calcium and vitamin D have low toxicity and are inexpensive, all patients starting glucocorticoids should also take a calcium and a vitamin D supplement prophylactically.

The new view: glucocorticoids cause bone loss mainly by reducing bone formation rather than by increasing bone resorption

Bisphosphonates are effective and recommended

The ACR[17] and UK[18] guidelines said that bisphosphonates are effective for preventing and treating bone loss in patients receiving glucocorticoids.

More recently, Stoch et al[20] evaluated the efficacy and safety of alendronate (Fosamax) 70 mg weekly for preventing and treating bone loss in patients on glucocorticoid therapy. At 12 months, bone mineral density in the lumbar spine, trochanter, and total hip had increased from baseline in the alendronate group and was significantly higher than in the placebo group. At the same time, levels of biochemical markers of bone remodeling were significantly lower than at baseline in the alendronate group.

For premenopausal women, postmenopausal women on estrogen replacement therapy, and men, the ACR[17] recommends risedronate (Actonel) 5 mg per day or alendronate 5 mg per day; for postmenopausal women not on estrogen, risedronate 5 mg per day or alendronate 10 mg per day is recommended.

Who should receive a bisphosphonate?

Fractures occur at a higher bone density with glucocorticoids than in postmenopausal osteoporosis

In men and postmenopausal women, the ACR[17] recommends a bisphosphonate for patients starting long-term glucocorticoid treatment (ie, expected to last 3 months or more) in doses of 5 mg or more per day of prednisone or its equivalent, irrespective of bone mineral density values.

In patients already taking glucocorticoids, a bisphosphonate should be started if the bone mineral density is below a certain threshold. The rationale for using bone mineral thresholds instead of giving bisphosphonates to all is that these drugs have potentially significant side effects and so should not be prescribed if not needed. The appropriate threshold at which intervention should be considered in glucocorticoid-treated patients is a matter of controversy. Based on evidence that fractures occur at a higher bone mineral density in glucocorticoid-treated patients than in postmenopausal women, the UK guidelines[18] recommend starting a bisphosphonate if the T score is less than –1.5 at the spine or hip, but the ACR[17] guidelines propose a T-score cutoff of –1.0. Whichever cutoff is chosen, its significance in terms of absolute fracture risk will differ according to the age of the patient. Therefore, use of T scores as an intervention threshold is not advisable.

The ACR and the UK guidelines both recommend measuring the bone mineral density by dual-energy x-ray absorptiometry at baseline (even though preventive therapy is not based on this value) and repeating it 6 months later and then yearly.

In premenopausal women, bisphosphonates should be used with caution, as they cross the placenta and are teratogenic in animals. Nevertheless, the ACR guidelines[17] state they can be given after appropriate counseling and instruction about contraception.

The UK guidelines[18] note that in the large clinical trials of alendronate and risedronate, the incidence of vertebral fractures was low in premenopausal women, indicating a very low fracture risk. Therefore, the UK guidelines state that bone-active drugs should be reserved for premenopausal women who have very low bone mineral density or who suffer fragility fractures or who have other strong risk factors for fracture.

In children and adolescents, the data are insufficient to produce evidence-based guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis. General measures include using the lowest effective dose of glucocorticoids for the shortest period of time, and considering alternate therapies, calcium and vitamin D supplementation, weight-bearing exercise, and proper nutrition.

Bisphosphonates are recommended when bone mineral density is falling despite these general measures and when "high-dose" glucocorticoids are likely to be used for a "prolonged" time, or in patients who have already had a fracture.[21]

Weekly doses may improve compliance

Risedronate is approved by the US Food and Drug Administration (FDA) for the prevention of glucocorticoid-induced osteoporosis, and both risedronate and alendronate are approved for its treatment.

The ACR guidelines recommend the FDA-approved (ie, daily) doses of alendronate and risedronate for glucocorticoid-induced osteoporosis. Most patients, however, are pre-

scribed weekly doses of these two agents, as compliance is much greater with this schedule of administration.

Estrogen is being used more selectively

The 2001 ACR guidelines said that, although there were no randomized controlled trials of hormone replacement (or testosterone) therapy to prevent glucocorticoid-induced bone loss, patients receiving long-term glucocorticoid therapy who are hypogonadal should be offered hormone replacement therapy.[17]

In 2002, the principal results of the Women's Health Initiative[22] showed that hormone replacement therapy with estrogen and progesterone was associated with a higher risk of breast cancer. Since then, the consensus has been that hormone replacement therapy should be restricted to women with menopausal symptoms or to older women who cannot tolerate other therapies or who express a strong preference for hormone replacement therapy despite being informed about potential adverse events.[23]

A role for testosterone?

Since a daily dose of more than 5 to 7.5 mg of prednisone increases the risk of gonadotropin and testosterone suppression,[24] testosterone replacement therapy has been used to treat glucocorticoid-induced osteoporosis in men.

In two placebo-controlled trials in men receiving glucocorticoid therapy for bronchial asthma or chronic obstructive pulmonary disease, testosterone therapy was associated with a significant 4% increase (95% CI 2–7) in bone mineral density in the lumbar spine.[25,26]

While these studies cannot be considered conclusive in view of their small size and the lack of fracture data, the Endocrine Society currently recommends that men with chronic obstructive pulmonary disease who are receiving glucocorticoids, are hypogonadal, and have no contraindications to androgen replacement therapy (eg, prostate cancer) be offered testosterone therapy to preserve lean body mass and bone mineral density.[27]

Calcitonin is not a first-line therapy

Neither the ACR nor the UK guidelines recommended calcitonin as first-line therapy.

A Cochrane systematic review[28] evaluated the data on the use of calcitonin to prevent and treat glucocorticoid-induced osteoporosis. Nine trials met the inclusion criteria, and included 221 patients randomized to receive calcitonin and 220 patients who received placebo. Calcitonin was more effective than placebo in preserving bone density in the lumbar spine, with a weighted mean difference of 2.8% (95% CI 1.4–4.3) at 6 months and 3.2% (95% CI 0.3–6.1) at 12 months. However, at 24 months, the lumbar spine bone mineral density was not statistically different between groups, nor was the relative risk of fractures. Calcitonin was given subcutaneously in one trial, in which it showed a substantially greater degree of prevention of bone loss than in the other trials, in which it was given nasally.

NEWLY APPROVED AND INVESTIGATIONAL AGENTS

Zoledronic acid once a year

Zoledronic acid (Reclast), a bisphosphonate given intravenously once a year, was approved for glucocorticoid-induced osteoporosis after the ACR and UK guidelines were published.

Zoledronic acid underwent a randomized multicenter, double-blind, active control trial[29] in 833 men and women, age range 18 to 85 years, who had glucocorticoid-induced osteoporosis (they had been treated with 7.5 mg per day or more of prednisone or its equivalent). Of these patients, 416 received a single infusion of 5 mg of zoledronic acid and daily oral placebo, and 417 received a single placebo infusion and daily oral risedronate 5 mg as an active control. All patients also received 1,000 mg of calcium and 400 to 1,000 IU of vitamin D per day. The study duration was 1 year.

The patient's fracture risk needs to be evaluated even after the glucocorticoid is stopped

Of those who had received a glucocorticoid for more than 3 months, those who received zoledronic acid had a significantly greater mean increase in lumbar spine bone mineral density compared with those in the oral risedronate group: 4.1% vs 2.7%, an absolute difference of 1.4% ($P < .0001$).

In those who had received a glucocorticoid for 3 months or less, those who received zoledronic acid also had a significantly greater mean increase in lumbar spine bone mineral density compared with those in the risedro-

nate group at 1 year: 2.6% vs 0.6%, a treatment difference of 2% ($P < .0001$).

Bone biopsy specimens were obtained from 23 patients, 12 in the zoledronic acid group and 11 in the risedronate group.[30] Qualitative assessment showed normal bone architecture and quality without mineralization defects. Apparent reductions in activation frequency and remodeling rates were seen when compared with the histomorphometric results in the zoledronic acid postmenopausal osteoporosis population.[31] The long-term consequences of this degree of suppression of bone remodeling in the glucocorticoid-treated patients are unknown.

The overall safety and tolerability of zoledronic acid in the glucocorticoid-induced osteoporosis population was similar to that in the postmenopausal osteoporosis clinical trial.[29,31] Adverse reactions reported in at least 2% of patients that were either not reported in the postmenopausal osteoporosis trial or were reported more frequently in the glucocorticoid-induced trial included the following: abdominal pain, musculoskeletal pain, nausea, and dyspepsia. The incidence of serious adverse events was similar in the zoledronic acid and the active control groups. In the zoledronic acid group, 2.2% of the patients withdrew from the study due to adverse events vs 1.4% in the active control group.

No oral glucocorticoid dose is safe with respect to bone

Teriparatide, a parathyroid hormone drug

Teriparatide (Forteo) consists of a fragment of the human parathyroid hormone molecule. It is given once daily by subcutaneous injection. It was also approved for treating glucocorticoid-induced osteoporosis after the current guidelines were written.

Teriparatide was compared with alendronate in a randomized, double-blind trial in patients with glucocorticoid-induced osteoporosis.[32] Entry criteria were treatment with at least 5 mg of prednisone per day for at least 3 months before screening and a T score of –2.0 or less in the lumbar spine, total hip, or femoral neck, or –1.0 or less plus one or more fragility fractures.

Eighty-three men and 345 women ages 21 or older were enrolled and randomized to receive injectable teriparatide 20 µg per day plus oral placebo or oral alendronate 10 mg per day plus injectable placebo. All of them also received calcium 1,000 mg per day and vitamin D 800 IU per day.

At 18 months, the bone mineral density had increased significantly more in the teriparatide group than in the alendronate group in the lumbar spine ($P < .001$) and in the total hip ($P < .01$). As expected, markers of bone turnover were suppressed in the alendronate group but were increased in the teriparatide group.

New vertebral fractures were found on radiography in 10 of 165 patients in the alendronate group vs 1 of 171 patients in the teriparatide group ($P = .004$). Clinical vertebral fractures occurred in 3 of 165 patients treated with alendronate but in none of the teriparatide-treated patients ($P = .07$). Nonvertebral fractures occurred in 8 of 214 patients treated with alendronate and 12 of 214 patients treated with teriparatide ($P = .362$). Three of 214 patients treated with alendronate suffered nonvertebral fragility fractures, compared with 5 of 214 patients treated with teriparatide ($P = .455$).

Denosumab, an antibody to RANK ligand

Denosumab (Prolia) is a fully human monoclonal antibody to RANK ligand. (Recall that glucocorticoids are associated with increases in RANK ligand and decreases in osteoprotegerin.) Denosumab is given subcutaneously in a dosage of 60 mg every 6 months. It was recently approved for the treatment of postmenopausal osteoporosis.

In a phase 2 study of denosumab[33] in men and women with rheumatoid arthritis (an independent risk factor for bone loss), the bone mineral density of the lumbar spine increased irrespective of whether the patients were treated with bisphosphonates and glucocorticoids.

ADHERENCE TO GUIDELINES IS POOR

Unfortunately, prevention and treatment in actual clinical practice still lag behind what is recommended in the current guidelines, even though multiple therapies are available.

In 2005, Blalock et al[34] expressed concerns about patients' knowledge, beliefs, and behav-

ior and the prevention and treatment of glucocorticoid-induced osteoporosis. They found that most patients taking oral glucocorticoids are not adequately educated about the prevention of osteoporosis, stating that "patients either are not being counseled or they are being counseled in a manner that is not sufficient to promote subsequent recall and behavior change."[34] They concluded that research is needed to develop effective ways to educate patients about how to prevent glucocorticoid-induced osteoporosis.

Also in 2005, Curtis et al[35] reviewed the records of managed-care patients taking glucocorticoids, comparing the prescription of antiresorptive therapy and the use of over-the-counter calcium or vitamin D or both in the periods 2001 to 2003 vs 1995 to 1998. The frequency of bone mineral density measurement in 2001 to 2003 had increased threefold compared with 1995 to 1998, and the use of a prescription antiresorptive drug had increased approximately twofold. However, only 42% of the patients underwent bone mineral density testing or were prescribed bone-protective medicine. The rates were lowest for men, at 25%.

A CALL TO ACTION

Evidenced-based guidelines exist to guide the clinician in an attempt to prevent the deleterious effects of glucocorticoids on bone. Physicians, physician assistants, nurse practitioners, and pharmacists need to coordinate their effects to ensure that adherence to these guidelines improves. Only then will the bone health of patients treated with glucocorticoids improve.

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