

Glucocorticoid-Induced Osteoporosis In Inflammatory Bowel Disease

Sheldon Lidofsky, MD, and Jeanette Smith, MD

Systemic glucocorticoid therapy is a mainstay in the treatment of active inflammatory bowel disease (IBD). However, glucocorticoids are associated with multiple side effects, of which bone loss resulting in glucocorticoid-induced osteoporosis and increase in fracture risk are predictable and debilitating complications.

Glucocorticoids exert multiple adverse effects on bone metabolism. They impair osteoblast growth, differentiation and function; reduce intestinal calcium absorption and increase renal calcium excretion, resulting in secondary hyperparathyroidism; and enhance osteoclast bone resorption.¹ Hypogonadism may result from glucocorticoid suppression of pituitary function. These drugs also decrease muscle mass and muscle strength, contributing to further bone loss by decreased physical activity.

Bone loss is most pronounced in the first six months of glucocorticoid use, especially in areas of trabecular bone (eg, vertebrae), which are the predominant sites of fracture.² The risk of fracture increases rapidly within the first 3 months of glucocorticoid therapy.³ However, both trabecular bone loss and cortical bone loss do occur over time.⁴ During the second year of treatment bone loss continues, but at a slower rate.⁴ Recovery after discontinuation of glucocorticoids may occur, but this is related to the dose of glucocorticoid used and its duration of use.⁴ Whatever bone mineral has been lost is unlikely to be fully restored. The increased risk of fracture in patients taking glucocorticoids does decline rapidly in the first year off of therapy.⁵

Significant bone loss and risk of fracture are thought to occur when the daily dose of prednisone is ≥ 7.5 mg. Men and women of all ages, including children, can lose bone while taking long-term glucocorticoid therapy.

Budesonide is a topically acting glucocorticoid that undergoes extensive first-pass metabolism in the liver and thus has low systemic bioavailability. It is available as an oral controlled-release formulation that delivers drug selectively to the ileocolonic region

of the gastrointestinal tract and is effective in patients with active ileocecal Crohn's disease (CD). A controlled trial included 272 patients with CD involving the ileum and/or ascending colon who were randomly assigned to once daily budesonide or prednisolone for 2 years at doses adapted to disease activity.⁶ Treatment with

Budesonide was associated with significantly less loss of bone mass compared with prednisolone in only those patients with active ileocecal CD who were steroid-naïve. This advantage was not seen with budesonide in patients previously exposed to glucocorticoids or those who were glucocorticoid-dependent.

GENERAL MEASURES TO PREVENT AND TREAT GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Many of the prevention and treatment strategies for glucocorticoid-induced bone loss are similar to those used to prevent and treat other causes of osteoporosis; i.e., lifestyle modifi-

cations, calcium and vitamin D supplementation, and in some patients, pharmacologic therapy to minimize further bone loss or increase bone density.

Glucocorticoids should be avoided, if possible, in the treatment of active IBD. If they cannot be avoided, use the lowest possible effective dose for the shortest possible period of time. Budesonide is preferred over other steroids in mild-moderate CD involving the ileum and/or proximal colon. Steroid-sparing agents should be considered, including azathioprine/6-mercaptopurine, methotrexate, and biologic agents (see Treatment of IBD in previous issue). Topical therapies are preferred to systemic therapies, if possible. Surgical intervention should be considered when appropriate (see articles on surgery in IBD in March 2009 *Medicine & Health/Rhode Island* by Pricolo, Sturrock and Klipfel). It is important to emphasize that steroids have no benefit in maintenance of remission in IBD.

If glucocorticoids cannot be avoided, general preventive measures should be initiated, including:

- avoidance of cigarette smoking and excessive alcohol use
- fall prevention measures
- weight-bearing exercises for at least 30 minutes five times weekly
- Calcium and vitamin D supplementation

CALCIUM AND VITAMIN D SUPPLEMENTATION

Glucocorticoids induce negative calcium balance by decreasing calcium absorption and increasing urinary calcium excretion. Calcium replacement may help restore positive calcium balance. The American College of Rheumatology (ACR) Task Force on Osteoporosis recommends that patients taking glucocorticoids maintain a calcium intake of 1000–1500 mg/day and

Vitamin D intake of 800 IU/day through either diet or supplements.⁷

In one study evaluating calcium and Vitamin D supplementation in patients with rheumatoid arthritis treated with low dose glucocorticoid therapy, those receiving calcium and Vitamin D supplementation gained bone in the LS spine

and trochanter at a rate of 0.7% and 0.8% per year, respectively.⁸ In those patients not receiving calcium or Vitamin D supplementation, bone was lost in the LS spine and trochanter at a rate of 2.0% and 0.9% per year, respectively.

It is important to assess Vitamin D levels in patients with IBD. If patients are Vitamin D deficient, pharmacologic doses of Vitamin D should be prescribed. Careful monitoring of the serum and urinary calcium concentration is essential in order to prevent the complications of hypercalcemia, hypercalciuria, and nephrolithiasis.

Hydrochlorothiazide may reduce the hypercalciuria associated with glucocorticoid therapy² and may represent a good

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choice for anti-hypertensive treatment in a hypertensive patient on glucocorticoids.

REPLACEMENT OF GONADAL SEX HORMONES

Glucocorticoids may reduce the production of sex steroids, resulting in hypogonadism. A significant gain in BMD in estrogen-treated postmenopausal women taking glucocorticoids was demonstrated compared with progressive bone loss in those taking glucocorticoids with no estrogen replacement therapy.⁹

However, long term clinical trials of combined estrogen-progestin therapy in postmenopausal women demonstrated increased risks of breast cancer, myocardial infarction, stroke, and venous thromboembolism.¹⁰ Therefore, estrogen is no longer viewed as a first-line drug for the prevention of postmenopausal osteoporosis.

The ACR Task Force does recommend oral contraceptive therapy for premenopausal women with oligomenorrhea or amenorrhea while taking glucocorticoids, if no contraindication exists.⁷

Because chronic glucocorticoid therapy can lower serum testosterone levels in men, those who take glucocorticoids regularly should have periodic serum testosterone determinations. Men with low serum levels of testosterone who are receiving glucocorticoids should receive testosterone replacement.⁷ If testosterone replacement is to be initiated, assessment for possible prostatic carcinoma with digital rectal examination and PSA at baseline and yearly thereafter should be performed. Prostatic carcinoma is an absolute contraindication to testosterone replacement.

BISPHOSPHONATES

Anti-resorptive therapy with the bisphosphonates alendronate and risedronate have been shown to be effective for both the prevention and treatment of glucocorticoid-induced bone loss. The effect of alendronate on glucocorticoid-induced osteoporosis was studied in a 2 year trial of 477 men and women on glucocorticoid therapy.¹¹ Significant increases in mean LS BMD by 2.1 % and 2.9 % were seen with 5 mg, and 10 mg, of alendronate per day, respectively. Femoral neck density significantly increased by 1.2 % and 1.0 % in the respective alendronate groups. Those receiving alendronate had fewer new vertebral fractures compared with placebo.

Risendronate has also been studied among men and women on glucocorticoids and showed significant increases in LS and hip BMD. The relative risk of vertebral fracture was reduced by 70 %.¹²

Oral bisphosphonates have the potential to cause esophageal and gastric ulcers. Osteonecrosis of the jaw is an infrequent, devastating side effect of bisphosphonate therapy.¹³ The majority of patients with this side effect received parenteral bisphosphonates in the setting of cancer treatment. It has also been rarely reported in patients receiving oral bisphosphonates. It can be triggered by dental surgery and by ill-fitted dentures.

Bisphosphonates are not approved for use in children. Premenopausal women and young men should not be treated with bisphosphonates in the absence of fracture history or evidence of accelerated bone loss.⁴ Caution must be exercised when considering bisphosphonates in premenopausal women. Bisphosphonates cross the placenta, and there is potential for harm to the fetus in

women who become pregnant while receiving or who have recently been treated with bisphosphonates.

PARATHYROID HORMONE

PTH stimulates bone formation as well as resorption, and intermittent administration stimulates formation of bone more than resorption. Increases in lumbar spine BMD and markers of bone formation have been observed among those treated with PTH.¹⁴ Markers of bone formation increased almost 150 % in the first 3 months of therapy, in contrast to markers of bone resorption, which increased only 100 %.

CALCITONIN

Calcitonin acts directly on osteoclasts to inhibit bone resorption. It causes a gain in bone mass of approximately 4-5 % when given parenterally at a daily dose of 100 IU.⁴ This medication has not received approval for use in glucocorticoid-induced osteoporosis. It can, however, be considered in patients who cannot tolerate bisphosphonates.

MANAGEMENT APPROACH

The AGA Medical Position Statement² recommends obtaining a DEXA scan in any patient with IBD with any of the following characteristics:

- prolonged glucocorticoid use (> 3 months consecutive or recurrent courses)
- history of low trauma fracture
- postmenopausal female or male age > 50
- hypogonadism

If T score > -1: - repeat DEXA in 2-3 years
- initiate basic preventive measures:
- adequate calcium/vitamin D;
- regular weight-bearing exercises;
- smoking cessation/ avoidance of excess alcohol;
- minimize glucocorticoids;
- consider correction of hypogonadism.

If T score - 2.5 to -1.0: - repeat DEXA in 2 years
- initiate basic preventive measures (as cited above)
- if prolonged glucocorticoids consider bisphosphonates and repeat DEXA in 1 year.

If T score <- 2.5/or if vertebral compression fractures regardless of DEXA - initiate basic preventive measures (as cited above)
- look for secondary causes of low bone density*
- bisphosphonate therapy; or
- refer to bone specialist

*CBC, serum calcium, alkaline phosphatase, creatinine, 25-OH vitamin D, SPEP, testosterone (males). Additionally, consider TSH, liver profile and celiac antibodies.

SUMMARY

Osteoporosis secondary to glucocorticoid use is a potentially preventable disorder.

It is the role of the physician to establish and maintain disease remission, minimize the use of glucocorticoids, and initiate measures to prevent and treat bone loss.⁴ The essentials of management include lifestyle modifications, nutritional interventions, and pharmacologic therapies. Bisphosphonates should be used when indicated.

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Sheldon Lidofsky, MD, is a Clinical Assistant Professor of Medicine, the Warren Alpert Medical School of Brown University.

Jeanette Smith, MD, is an Instructor, Department of Medicine, The Warren Alpert Medical School of Brown University.

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The authors have no financial interests to disclose.

Discussion of off-label or investigational drug: Miacalcin

CORRESPONDENCE

Sheldon Lidofsky, MD
phone: (401) 421-8800
email: Sheldon_Lidofsky@brown.edu

