Inhaled corticosteroid–induced bone loss and preventive strategies

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Systemic corticosteroids are known to cause adverse effects on bone loss and, with long-term use, may result in osteoporosis. There is evidence that inhaled corticosteroids at moderate to high doses may also induce bone loss. This article discusses the effects of inhaled corticosteroids on bone formation and resorption. It also offers preventive strategies to minimize bone loss associated with long-term use of inhaled corticosteroids.

(Key words: asthma, inhaled corticosteroids, osteoporosis, bone loss)

Inhaled corticosteroids are the mainstay in the treatment of asthma, allowing effective control of symptoms without the serious side effects associated with systemic corticosteroids. The efficacy of inhaled corticosteroids in asthma treatment is dose-dependent, allowing greater anti-inflammatory effect with higher doses. Patients with severe asthma are often taking very high doses of inhaled corticosteroid.[1]

There is concern that high-dose inhaled corticosteroids may have adverse effects on bone metabolism. This concern arises from the frequency with which osteoporosis is known to occur with long-term use of oral steroids.[2] Nearly 50% of patients may have osteoporotic fractures develop as a result of oral corticosteroid therapy if adequate prevention and treatment of this complication are not initiated immediately.[3]

Other factors to consider are differences between various types of inhaled corticosteroids (*Table*). Corticosteroids differ between each other in potencies, suppression of the hypothalamus-pituitary-adrenal axis, and degree of systemic absorption. The dose of each of the inhaled corticosteroids that is systemically absorbed needs to be established. Whether all inhaled corticosteroids at equivalent doses are associated with the same risk is unknown.

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Mechanisms of corticosteroid-induced bone changes

The mechanism of corticosteroid-induced bone loss is complex. Adult bone matrix reflects a constant balance of activity between bone-forming osteoblasts and bone-breakdown cells (osteoclasts).[4] A change in this equilibrium may result in reduction of bone mass, resulting in osteoporosis and risk of fracture. Corticosteroids affect both bone formation and resorption. Corticosteroids decrease osteoblast activity, which results in decreased matrix synthesis and a decreased active life span of osteoblasts. This results in a decrease in the bone mass of mainly the axial skeleton (that is, vertebrae), as the vertebrae contain more metabolically active trabecular bone than cortical bone. This effect with corticosteroids has been observed using biochemical markers of bone turnover, particularly serum osteocalcin, which decreases in a dose-dependent way within 4 days of starting corticosteroid therapy.[5]

Other markers of bone formation include serum levels of alkaline phosphatase, osteocalcin, procollagen type 1 carboxyterminal and aminoterminal propeptide, and procollagen type 3 aminoterminal propeptide.[4] Corticosteroids also effect osteoclast activity, leading to an increase in bone resorption. Markers for the increase in osteoclast activity include urinary levels of hydroxyproline, urinary or serum pyridinium cross-links, urinary collagen type 1 cross-linked N-telopeptide, urinary collagen type 1 cross-linked C-telopeptide, and serum carboxyterminal telopeptide of type 1 collagen.[4] Bone formation markers are considered to be more sensitive than bone resorption markers in assessing the effects of corticosteroids, with osteocalcin being the most sensitive, specific, and reproducible.[4]

Review of clinical studies

Pediatric

Prolonged use of systemic corticosteroids are known to suppress linear growth in children.[4] Asthma itself seems to have a negative effect in delaying puberty and reducing growth height, and it should also be considered when evaluating the effect of corticosteroids on bone.[4] In addition, there have been a number of studies evaluating the effects of inhaled corticosteroids on growth rate and biochemical markers, as well as bone mineral density (BMD) in children.

Agertoft and Pedersen[6] evaluated short-term knemometry (a measurement of velocity of lower leg growth) and 24-hour urine cortisol excretion in 48 children aged 6 to 12 years. One group of children received treatment with either fluticasone propionate, 200 μg/d; budesonide, 200 μg/d; or placebo in a randomized, crossover manner. A second group of children received either fluticasone propionate, 400 μg/d; budesonide, 400 μg/d; or placebo in a similar manner. Each treatment period was 15

Table
Inhaled Corticosteroids

Drug*	No. of puffs		
	Low dose	Medium dose	High dose
■ **Beclomethasone dipropionate** (Vanceril, Beclovent) 42 μg per puff	4 to 12	12 to 20	>20
■ **Budesonide** (Pulmicort Turbuhaler) 200 μg per puff	1 to 2	2 to 3	>3
■ **Flunisolide** (AeroBid) 250 μg per puff	2 to 4	4 to 8	>8
■ **Fluticasone propionate** (Flovent)			
44 μg per puff	2 to 6	6 to 15	>15
110 μg per puff	2	2 to 6	>6
220 μg per puff			>3
■ **Triamcinolone acetonide** (Azmacort) 100 μg per puff	4 to 10	10 to 20	>20

*Drugs are listed by generic names, with trade names in parentheses.

to 18 days. Knemometry was used to measure the lower leg length twice a week, and 24-hour cortisol excretion was measured at the end of each treatment period. No difference was seen in rate of lower leg growth within each group between budesonide or fluticasone; however, growth rate was significantly lower in the group receiving budesonide at a dosage of 400 μg/d than in the group receiving the placebo. At this dose—fluticasone propionate, 400μg/d, and budesonide, 400 μg/d—there resulted a significant reduction in urinary cortisol excretion compared with that with placebo.

Konig and associates[7] evaluated bone metabolism in 18 asthmatic children (aged 4 to 17 years) who were treated with inhaled beclomethasone dipropionate (400 μg/d to 800 μg/d) for at least 6 months. Each child was controlled with an age- and sex-matched patient with asthma who was not receiving corticosteroid therapy. Serum levels of calcium, total alkaline phosphatase, bone-specific alkaline phosphatase, parathyroid hormone, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D were measured, as was BMD. The study found no significant differences in the measured serum markers between the treated groups and their age-matched cohort. Further, no significant difference was seen on bone densitometry. The study concluded that inhaled beclomethasone does not reduce bone mineralization or increase bone resorption in children with asthma.

These results were confirmed in a later study by Martinati and coworkers,[8] who studied the effects of inhaled corticosteroids on cortical and trabecular bone mass in 64 asthmatic prepubertal subjects (aged between 5 and 10 years) who were treated with beclomethasone dipropionate, 150 μg/d to 600 μg/d, or cromolyn sodium, 30 mg/d for 6.7 months. Lumbar spine bone mass was measured by dual-energy x-ray absorptiometry (DEXA). The DEXA measurements showed no difference in trabecular bone mass in children who received beclomethasone versus children who received cromolyn sodium. Thus, it appears that inhaled corticosteroids at low doses do not induce osteoporosis in children.

Adults

A number of short- and medium-term studies have evaluated the effects of inhaled corticosteroids on biochemical bone markers in both healthy volunteers and asthmatic patients.[9-12] During study periods of 2 to 4 weeks, most studies showed that levels of various markers significantly changed on inhaled corticosteroid therapy, with the magnitude of effect being dose-related.

Kerstjens and colleagues[13] conducted two studies on the short-term and long-term effects of inhaled corticosteroids on bone metabolism of patients with asthma or chronic obstructive pulmonary disease. In the first pilot study, 15 patients (mean age, 41.1 years) received at least 800 μg/d of beclomethasone dipropionate (≥20 puffs per day). Serum levels of alkaline phosphatase, osteocalcin, procollagen type 1 carboxy terminal propeptide (PICP), and type 1 collagen carboxy terminal telopeptide (ICTP), and urine level of hydroxyproline were measured at baseline and after 4 weeks of inhaled beclomethasone therapy. In the second long-term, double-blind study, 70 patients (mean age, 40 years) received beclomethasone diproprionate, 800 μg/d, while serum PICP and ICTP were measured at baseline and after 2.5 years of treatment. Although the 4-week pilot study revealed a decrease in serum osteocalcin levels and an increase in serum PICP levels, the long-term study showed no significant changes in serum levels of PICP and ICTP of patients treated with inhaled corticosteroids compared with patients treated without inhaled corticosteroids. This finding suggests that the clinical significance of short-term changes in metabolic markers with inhaled corticosteroids is not clear, because long-term studies result in no changes in these markers. Hence, these markers cannot be used as surrogate indicators for bone density to predict risk of developing osteoporosis.

Luengo and colleagues[14] conducted a case-control study on 48 asthmatic adults (mean age, 56 years) treated with inhaled corticosteroids—beclomethasone or budesonide (300 μg to 1000 μg) for

more than 1 year (mean duration of treatment, 10.6 years). Twenty-four patients had received one to six short courses of oral corticosteroids while 7 patients had received oral corticosteroids (mean daily dose of 6.2 mg of prednisone) for 2 to 15 years more than 4 years before the bone densitometry measurements of this study. Vertebral BMD measured by DEXA was obtained at baseline and at 2 years in the asthmatic patients and their age-matched controls. The findings indicated no significant differences in BMD loss between the group using inhaled corticosteroid and the control group; both groups showed a decrease in BMD over 2 years. These data suggested that inhaled corticosteroids at mean doses up to 662 μg/d do not further increase bone mass loss beyond that expected from natural bone mass loss.

Prevention of inhaled corticosteroid–induced bone loss

To date, there are no documented treatment guidelines for prevention of inhaled corticosteroid–induced bone loss. All recommendations have been geared toward oral corticosteroids.[15] Therefore, we opt to suggest that the general recommendations for prevention and treatment of glucocorticoid-induced osteoporosis be considered in patients taking medium to high doses of inhaled corticosteroids.[15]

Calcium and vitamin D

The American Rheumatologists Association recommends that all patients on glucocorticoid therapy have an adequate intake of calcium and vitamin D.[15] A daily calcium intake of 1500 mg is recommended, either obtained through dietary intake or calcium supplementation. In addition, vitamin D (either 800 IU/d or 50,000 IU three times a week) or calcitriol (0.5 μg/d) should be added.

Hormone replacement therapy

Postmenopausal women receiving medium to high doses of inhaled corticosteroids should receive estrogen therapy. Estrogens increase bone mass and reduce the risk of fractures related to osteoporosis. Women with a uterus should also receive a progesterone for 12 to 14 days per month to reduce the risk of endometrial hyperplasia. Women at high risk for breast cancer or having a history of breast cancer should consider raloxifene hydrochloride, an estrogen-receptor antagonist. In a multicenter, randomized, placebo-controlled study of raloxifene in early postmenopausal women with osteoporosis, bone density increased by 2.1% to 2.4% in the femoral neck and 2.6% to 2.7% in the spine compared with those taking placebo.[16] However, the efficacy of raloxifene in patients receiving inhaled corticosteroids has not been published.

Bisphosphonates

The actual mechanism of action of bisphosphonates is poorly understood; however, they are inhibitors of bone resorption (reduction of number of osteoclasts) that are used in treatment of Paget's disease, hypercalcemia, and osteoporosis.[17] Many bisphosphonates (such as alendronate sodium, cyclic etidronate disodium, and pamidronate disodium) have been evaluated in corticosteroid-induced bone loss. Intermittent cyclical etidronate sodium (400 mg daily for 2 weeks) and calcium (500 mg/d for 11 weeks) was studied and resulted in an increase in BMD of lumbar spine by 1.8% ($P<.001$) at both 6 months and 12 months.[18] Intermittent etidronate disodium (400 mg/d for 14 days) and calcium (500 mg/d for 76 days) prevented loss of vertebral and trochanteric bone in 141 patients aged 19 to 87 years treated with high-dose oral prednisone (>7.5 mg/d).[19] The mean BMD of the lumbar spine and trochanter in the group receiving etidronate increased by 0.61% and 1.46%, respectively, as compared with a decrease of 3.23% and 2.74%, respectively, in the group receiving the placebo.

In a randomized, placebo-controlled study of adults receiving long-term glucocorticoid therapy, patients were treated with alendronate, 5 mg/d to 10 mg/d for 48 weeks.[20] The mean BMD of the lumbar spine in these patients increased by 2.1% and 2.9% ($P<.001$); the femoral neck BMD increased by 1.2% and 1% ($P<.01$) in the alendronate-treated group as compared with the placebo group.

In an early postmenopausal intervention cohort study of 1202 women, aged 45 to 59 years, treated with alendronate, 2.5 mg/d and 5 mg/d for 2 years, there was an increased response in spine and hip BMD of 2% to 4% over 2 years.[21]

Comment

Patients taking moderate to high doses of inhaled corticosteroids may be at increased risk for long-term bone loss, especially if used for a prolonged time. It remains to be established whether inhaled corticosteroid–induced bone changes are clinically important. Although no specific guidelines are available, it would seem prudent to consider preventive measures such as calcium and vitamin D supplementation in patients taking moderate to high doses of inhaled corticosteroids (*Table*). Patients with additional risk factors, such as a postmenopausal state, should consider estrogen replacement therapy. If high doses of inhaled corticosteroids are used, a screening bone DEXA scan may be indicated to see if more aggressive therapy is needed.

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