

# Osteoporosis in the corticosteroid-treated patient with asthma

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Osteoporosis affects 40% of white women older than 45 years of age and 15% of white men older than 50 years of age, resulting in approximately 1.5 million annual fractures in the United States. Systemic corticosteroid therapy increases the probability of osteoporosis, even with alternate-day dosing and with dosages sufficiently low so as not to affect the hypothalamic-pituitary-adrenal axis. Inhaled corticosteroid therapy may affect bone density if high-dose therapy is given to select individuals. The potential of increasing osteoporosis with inhaled corticosteroid asthma therapy is a concern because of the availability of more potent inhaled corticosteroid agents and recommendations that inhaled corticosteroid therapy be initiated earlier in the course of asthma. This article provides suggestions, on the basis of the medical literature and consensus of the authors when specific information was not available, for assessing and treating osteoporosis in subjects with asthma. Suggested risk categories are "low risk" (inhaled corticosteroid dosage of  $\leq 800$   $\mu$ g of beclomethasone dipropionate [BDP]/day in adults or  $\leq 400$   $\mu$ g BDP or equivalent in children), "moderate risk" (inhaled BDP  $> 800$   $\mu$ g/day in adults or  $> 400$   $\mu$ g/day in children), and "high risk" (systemic corticosteroid therapy 4 times a year or daily or alternate-day systemic corticosteroid therapy). Dosage of nasal corticosteroid probably should be added to the orally inhaled corticosteroid for total burden of inhaled corticosteroid. Potential treatment strategies based on risk factors and bone density if indicated are offered to assist physicians treating patients with asthma. (J Allergy Clin Immunol 1998;102:353-62.)

**Key words:** Osteoporosis, asthma, corticosteroid, inhaled corticosteroid, bone density

### Abbreviations used

BDP: Beclomethasone dipropionate  
DXA: Dual-energy x-ray absorptiometry  
QCT: Quantitated computer tomography  
TSH: Thyroid-stimulating hormone

Corticosteroids are the most effective antiinflammatory medication for the treatment of asthma. Systemic corticosteroid therapy is associated with significant adverse effects, including the promotion of osteoporosis. In contrast to systemic corticosteroid therapy, inhaled corticosteroids provide effective therapy of asthma with few adverse effects.<sup>1</sup> The effects of inhaled corticosteroid therapy on bone metabolism are not certain but are a concern with the increasing use of moderate and high doses for longer periods of time. The relative risk of osteoporosis for different inhaled corticosteroid preparations and dosages has not been defined. Research is delineating the best procedures for diagnosis, prevention, and treatment of osteoporosis.<sup>2,3</sup> The purposes of this paper are to review what is known about osteoporosis risk factors and to recommend methods of prevention, diagnosis, and treatment of osteoporosis for the allergist-immunologist.

## DEFINITION AND SIGNIFICANCE OF OSTEOPOROSIS

Osteoporosis is a "disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk."<sup>4</sup> The condition is characterized by loss of both mineral and matrix from bone with the ratio of the two remaining normal. The result is decreased strength and increased tendency to fracture from minimal trauma or stress. The most common fracture sites are the vertebra, wrist, hip, proximal humerus, and pelvis. The clinical significance of osteoporosis is a product of the morbidity and mortality that accompanies these fractures.

## EPIDEMIOLOGY AND RISK FACTORS

Osteoporosis is a common clinical problem. Forty percent of white women older than 45 years of age and 15% of white men older than 50 years of age have osteoporosis and are at risk of a fracture.<sup>5-8</sup> Osteoporosis contributes to approximately 1.5 million annual fractures in the United States: 700,000 in the vertebrae; 250,000 in the distal forearms; 250,000 in the hips; and 300,000 in other distal limb

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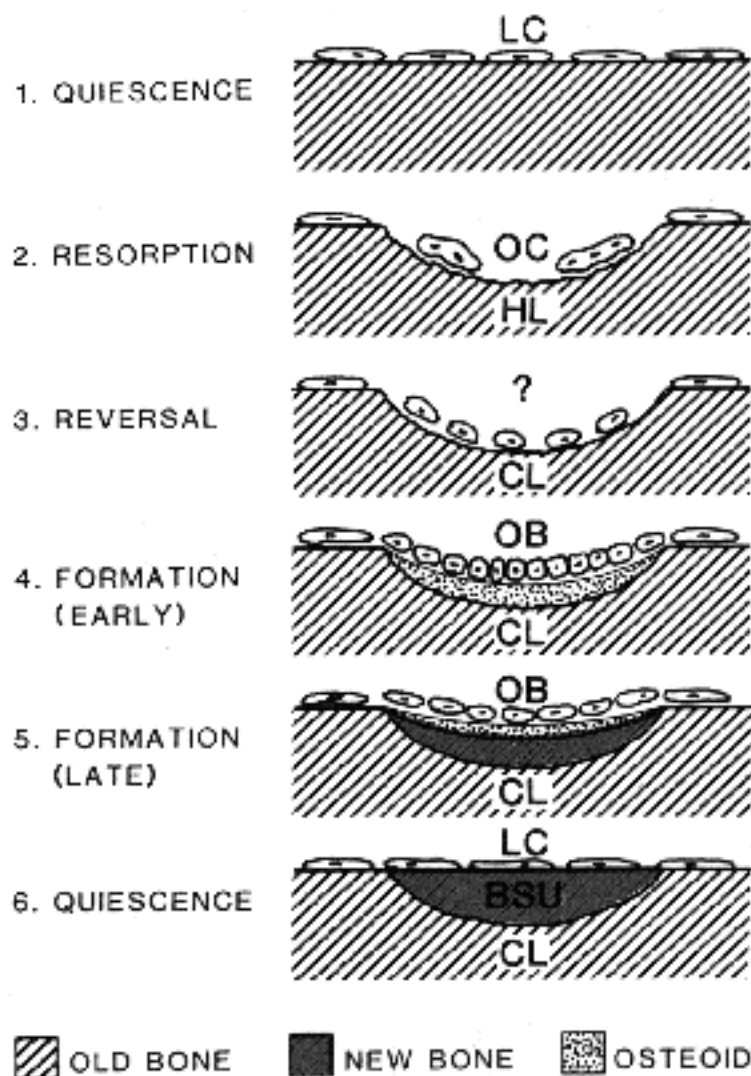


**FIG 1.** Life history of bone remodeling. This diagram shows the life history of a single bone remodeling unit, with construction of a single new bone structural unit (BSU). 1, Quiescent surface covered by flat lining cells (LC). 2, Resorbing surface with osteoclasts (OC) lying in a Howship's lacuna (HL). 3, Reversal phase, during which unnamed mononuclear cells of uncertain origin smooth over the resorbed surface and deposit the cement substance, seen as the cement line (CL) in histologic sections. 4, Early forming surface with young osteoblasts (OB), which have deposited a thick layer of osteoid on the cement line; mineralization has not yet begun. 5, Late-forming surface with old osteoblasts, which have almost finished making osteoid; there is now a layer of new mineralized bone between the cement line and the osteoid seam. 6, Restoration of the quiescent surface with completion of the cycle of remodeling. The cavity has been completely refilled to form a new bone structural unit. The coordinated team of precursor cells, osteoclasts, reversal cells, and osteoblasts appearing sequentially in the same location to build a single bone structural unit comprise a single bone remodeling unit. This diagram depicts the entire bone remodeling process from start to finish. (Reprinted from the *Journal of Bone and Mineral Research* 1986;1:15-21 [Dempster et al.] with permission of the American Society for Bone and Mineral Research.)

sites.<sup>4,9</sup> Estimates are that 1.7 million hip fractures occurred worldwide in 1990 and, by the year 2050, the number will reach 6.3 million.<sup>10,11</sup> The estimated direct medical costs for the treatment of hip fractures alone are greater than \$9 billion per annum in the United States.<sup>12</sup> These costs per year include 250,000 to 330,000 hospitalizations, more than 3.4 million hospital bed days, and over 60,000 nursing home admissions. The indirect costs are even greater, with 7 million restricted activity days among

noninstitutionalized subjects. One third of affected subjects become incapable of living independently.<sup>6</sup>

Although osteoporosis is usually considered a disease of women, both sexes lose bone mass with aging. Peak bone mass is achieved at about 30 to 35 years of age for cortical bone and 5 to 10 years earlier for trabecular bone. Bone mass, after peaking, declines for the remainder of life because of an imbalance in remodeling (bone resorption exceeds bone formation) (Fig 1). Bone loses

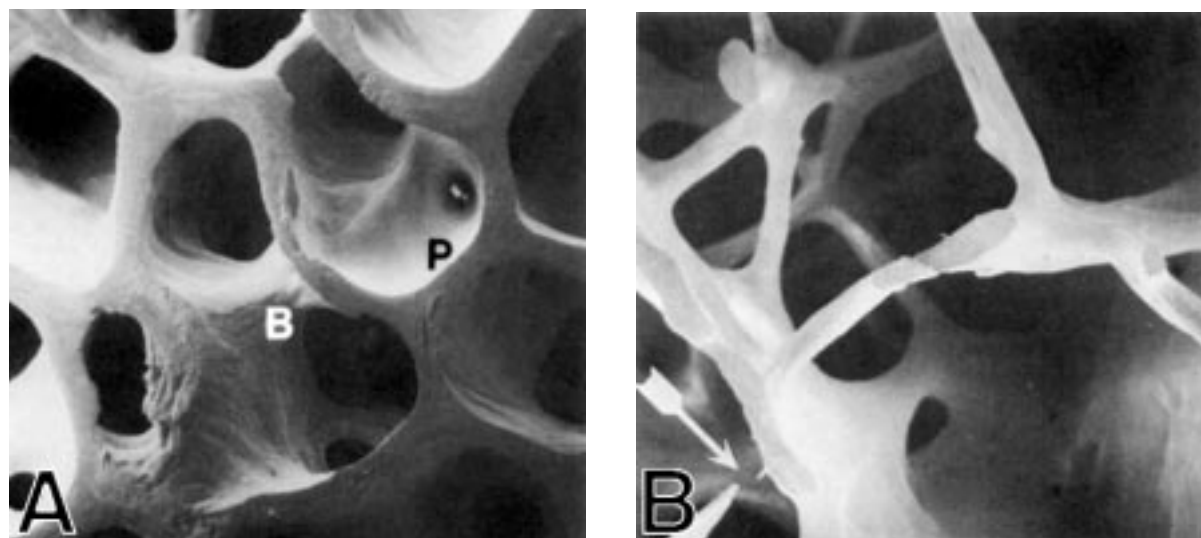


**FIG 2. A**, Low-power scanning electron micrograph of an iliac crest (trabecular bone) biopsy specimen from a normal 1-year-old boy. **B**, Low-power scanning electron micrograph of an iliac crest (trabecular bone) biopsy specimen from an osteoporotic 47-year-old woman. Note the thin walls and bone fragments. Note the thinning of trabecular walls and the fractures. (Reprinted with permission of the publisher from Dempster DW, et al. A simple method for correlative light and scanning electron microscopy of human iliac crest bone biopsies: qualitative observations in normal and osteoporotic subjects. *J Bone Min Res* 1986;1:15-21).

both mineral and organic matrix but retains its basic, histologic organization (Fig 2 A and B). Cortical bone loss for both women and men is linear starting at about 40 years of age. The annual rate of loss is 0.5% to 1.0%. Trabecular bone loss starts at about 35 years of age for both genders.<sup>12,13</sup> The annual rate of loss is 1.0% to 1.2% for men and 1.0% to 4.0% for women; women experience an accelerated postmenopausal bone loss up to 10% per year for 3 to 7 years after menopause.<sup>9,14,15</sup>

In addition to gender, genetic background and ethnicity influence peak bone density. Twin and family studies suggest that genetic factors explain as much as 75% of the variation in age-specific bone density.<sup>10,16,17</sup> Whites and probably Asians have the greatest risk for osteoporosis, Mexican Americans have less risk, and African Americans have the least risk.<sup>9,14,18,19</sup> There are many additional factors that negatively affect bone density (Table I).

The risk for osteoporosis-related fractures is greatly increased by medications, diseases, or both that accelerate bone resorption or inhibit bone formation. The most common cause of secondary osteoporosis is corticosteroid therapy.<sup>20</sup>

### CORTICOSTEROID-INDUCED OSTEOPOROSIS

Corticosteroid-induced osteoporosis has been recognized since 1932 when Cushing described bone loss and skeletal fracture in hypercortisolism. Approximately 30% to 50% of subjects chronically treated with systemic corticosteroids have osteoporosis.<sup>21</sup> Prednisone dosages of less than 10 mg of prednisone per day result in a 3% to 16% reduction in the bone mineral content of the lumbar spine.<sup>22-24</sup> The most rapid bone loss occurs during

**TABLE I.** Risk factors for osteoporosis

|                                                                                                         |
|---------------------------------------------------------------------------------------------------------|
| • Gender, race, family history                                                                          |
| • Reduced calcium ingestion, particularly during childhood and adolescence                              |
| • Sedentary lifestyle                                                                                   |
| • Cigarette smoking                                                                                     |
| • Medical therapy with corticosteroids, phenytoin, cyclosporin, warfarin, heparin, and antigonadotropin |
| • Supraphysiologic doses of thyroid supplement                                                          |
| • Parathyroid hormone excess                                                                            |
| • Premature natural or surgical menopause                                                               |
| • Amenorrhea                                                                                            |
| • Delayed puberty and hypogonadism (male and female)                                                    |
| • Low body weight, slight build                                                                         |
| • Excessive alcohol intake                                                                              |
| • Inflammatory diseases, such as rheumatoid arthritis or systemic lupus erythematosus                   |
| • Systemic mast cell disorders                                                                          |

**TABLE II.** Major mechanisms by which corticosteroids affect bone<sup>27</sup>

|                                                                   |
|-------------------------------------------------------------------|
| • Decrease in intestinal absorption of both calcium and phosphate |
| • Increase in urinary calcium excretion                           |
| • Secondary hyperparathyroidism                                   |
| • Reduction of circulating estrogen and testosterone              |
| • Inhibition of osteoblast proliferation and function             |

the first 6 to 12 months of systemic corticosteroid therapy,<sup>25</sup> but bone loss continues at a lower rate with more prolonged therapy.<sup>26</sup> Corticosteroids cause bone loss primarily by inhibiting bone formation. Corticosteroid-induced bone loss occurs more rapidly in skeletal areas

**TABLE III.** Selected biochemical markers of bone turnover<sup>85-87</sup>

| Markers of bone resorption                    | Markers of bone formation                      |
|-----------------------------------------------|------------------------------------------------|
| Serum                                         |                                                |
| C-telopeptide of type I procollagen           | Total and bone-specific alkaline phosphatase   |
| Cross-linked N-telopeptide of type I collagen | Carboxy terminal propeptide of type I collagen |
| Deoxypyridinoline crosslinks                  | Osteocalcin                                    |
| Urine                                         |                                                |
| Deoxypyridinoline crosslinks                  |                                                |
| Hydroxyproline                                |                                                |
| Hydroxyllysine glycosides                     |                                                |
| Pyridinoline crosslinks                       |                                                |
| Cross-linked N-telopeptide of type I collagen |                                                |
| C-telopeptide of type I collagen              |                                                |

with the highest rate of bone turnover, with trabecular bone loss rates exceeding those of cortical bone. Trabecular bone-rich areas include the vertebral bodies, the femoral heads, ribs, proximal humeri, and distal radii. The mechanisms by which corticosteroids affect bone are listed in Table II.<sup>27</sup>

Every individual receiving either oral or topical inhaled corticosteroid therapy is at risk for bone loss regardless of age, ethnicity, gender, or other risk factors for noncorticosteroid-induced osteoporosis. For example, individuals who ordinarily would not be considered at high risk for osteoporosis, including African Americans, men, and children, are at risk for corticosteroid-induced osteoporosis. The lack of a measurable effect on the hypothalamic-pituitary-adrenal axis does not equate with lack of effect on bone metabolism. In one study every other day systemic corticosteroid therapy, which preserves the hypothalamic-pituitary-adrenal axis, did not prevent accelerated bone loss.<sup>28</sup> Oral prednisone (7.5 mg/day), which has no appreciable effect on the hypothalamic-pituitary-adrenal axis,<sup>22</sup> resulted in a 3% annual loss of bone in one study.

Inhaled corticosteroids are an effective therapy for asthma. The 1997 revision of the National Heart, Lung, and Blood Institute "Guidelines for the Diagnosis and Management of Asthma" recommends the use of such therapy for persistent asthma.<sup>1</sup> Preliminary evidence suggests that lung function both in children and adults is maximized with the initiation of inhaled corticosteroid therapy when asthma is diagnosed.<sup>28-30</sup> No epidemiologic data to date prove that inhaled corticosteroid therapy is associated with an increased incidence of osteoporosis.<sup>31-34</sup> Data suggest that inhaled corticosteroid therapy negatively affects bone density, with the daily dose having more of an effect than the cumulative dose or duration of therapy.<sup>31,32</sup> Inhaled corticosteroid therapy decreases serum osteocalcin, a chemical marker of bone.<sup>35,36</sup> It is not known whether there is a threshold

dose below which bone loss does not occur. Because 600 to 800 µg/day of inhaled beclomethasone dipropionate (BDP) probably slows growth rate in children, it is reasonable to expect some effect on bone metabolism at or above this dosage.<sup>29,36</sup>

The role of nasal corticosteroid therapy in modifying bone metabolism is even less defined. Growth velocity in children is transiently reduced with nasal steroid therapy in one study with BDP (336 µg/day).<sup>37</sup> Another study showed reduced serum osteocalcin in adults treated with nasal corticosteroids.<sup>38</sup> Thus nasal corticosteroids may contribute to the total effect on bone metabolism.

## ASSESSMENT

The purpose of bone density assessments is to identify individuals at risk for a fracture and to monitor the treatment of osteoporosis. Various techniques are available to assess bone density. Dual-energy x-ray absorptiometry (DXA) and quantitated computed tomography (QCT) are most widely used. Presently, DXA is preferred over QCT because it is less expensive, more accurate, and requires less radiation exposure.<sup>2,39,40</sup> The utility of a test to monitor a condition is limited by the precision of the test. The magnitude of change in a monitored value must be 2.8 times the precision of the test before the change can be identified with a 95% confidence level. The precision of DXA is 1% to 3%. Thus if the rate of bone loss is 1% to 2% per year, repeat bone density assessments would not be of value any more often than 2 to 3 years. However, if the rate of loss is 5% to 10% per year,<sup>23,24</sup> as sometimes occurs with low-dose systemic corticosteroid therapy, then repeat testing as often as every 6 months could be useful. Factors that may affect precision and accuracy of DXA include bone marrow fat (resulting in falsely low bone density) and anatomic changes of the axial skeleton, such as compression fractures, scoliosis, osteophytes, intervertebral disc space narrowing, and previous laminectomy (resulting in falsely elevated bone density).

DXA values are interpreted by comparing the number of standard deviations above or below the mean density to that of a young, adult, gender-matched population (T score). The Z score is the number of SDs above or below a population matched for age and gender. The Z score compares an individual with his or her peers, and the T score compares an individual with his or her ideal. Osteoporosis is defined as a T score more than 2.5 SDs below the mean.<sup>39</sup> Osteopenia is defined as a T score between -2.5 and -1.0. The relative risk for a fracture doubles for every decrease of 1 SD in bone mass. The percentage of the general US female population with a T score less than -2.5 is approximately 2% between 30 and 50 years of age, 15% between 50 and 60 years of age, 31% between 60 and 70 years of age, 44% between 70 and 80 years of age, and 70% for subjects older than 80 years.<sup>39</sup> Fracture threshold currently applies to measurement in postmenopausal women as similar data have not been developed in other risk populations.<sup>12</sup> It cannot be assumed that the risks are identical in different populations with the same bone density measurements. Some evidence suggests that the frac-

ture threshold is different for corticosteroid-related osteoporosis and involutional osteoporosis.<sup>41</sup>

The regulation of bone mass is a complex, dynamic relationship between bone formation by osteoblasts and bone resorption by osteoclasts. A number of serum biochemical markers have been described that may reflect the balance between osteoblast and osteoclast function (Table III). Inhaled corticosteroid therapy negatively affects some of these markers in a dose-dependent manner, with a threshold of 800 to 2000 µg/day of BDP or equivalent. The clinical significance of changes in these markers has not been established.

## **THERAPIES THAT AFFECT BONE FORMATION OR RESORPTION**

The development of effective therapies for osteopenia/osteoporosis has increased the importance of diagnosing this condition before the development of fractures. Current therapies reduce bone resorption. Most of the evidence supporting the effectiveness of these therapies has been developed in postmenopausal women, and it is not known whether these treatments are as effective in corticosteroid-induced osteoporosis or in other age groups.

### **Calcium**

Corticosteroids reduce calcium absorption from the gastrointestinal tract and increase calcium loss in the urine. If there is no contraindication, such as hypercalciuria or ureterolithiasis, everyone should receive calcium supplementation or dietary counseling to maintain a total daily dose of elemental calcium as follows<sup>43</sup>: 800 mg/day for 1 to 10 years of age, 1200 mg/day for 11 to 24 years of age, 1200 mg/day during pregnancy and lactation, 1000 mg/day for adults greater than 24 years of age, 1500 mg/day for postmenopausal women, and 1500 mg/day for adults at risk of osteoporosis.

### **Vitamin D**

Vitamin D is beneficial for both treatment and prevention of corticosteroid-induced bone loss.<sup>44</sup> 25-OH vitamin D levels should generally be maintained in the upper limits of the normal range, with supplement dosages of 400 to 800 U/day (most multivitamin supplements contain 400 U; vitamin D is available as 400 and 800 U doses). A dosage of 7000 IU vitamin D/day, usually achieved by giving 50,000 IU once a week, may be necessary in vitamin D deficiency and requires that serum levels of 25-OH vitamin D be monitored after 3 months of therapy to avoid vitamin D toxicity. Doses of 50,000 IU 2 to 3 times per week are not recommended in patients with normal 25-OH vitamin D levels. Such dosages often result in hypercalciuria, hypercalcemia, or both.<sup>45</sup> A more biologically active form of vitamin D, 1,25 (OH)<sub>2</sub> vitamin D or calcitriol, is available. Osteoporosis therapy with calcitriol is controversial. One study showed reduced loss of bone in the lumbar spine in systemic corticosteroid-treated subjects when calcitriol was combined with calcitonin and calcium. Calcitriol and calcium were also effective treatments but were less effective than the 3 agents combined.

Neither treatment prevented bone loss in the femoral neck, and 25% of treated subjects experienced hypercalciuria, hypercalcemia, or both.<sup>46</sup> Thus the side effects caused by calcitriol limit its use.

### **Thiazide diuretics**

Thiazide diuretics and sodium restriction improve gastrointestinal absorption of calcium and reduce urinary excretion of calcium. Systemic corticosteroids reduce calcium absorption, which results in an increase in parathyroid hormone. The positive calcium balance effects of thiazide diuretics and sodium restriction would be predicted to ameliorate the secondary hyperparathyroidism resulting from corticosteroid therapy. Thiazide therapy has not been assessed in corticosteroid-treated individuals. However, thiazide diuretic therapy (hydrochlorothiazide 25 mg/day) has been associated with higher bone density and a modest reduction in fracture risk in subjects not receiving corticosteroids.<sup>47</sup> Thiazide diuretics, if indicated, should be used in combination with potassium-sparing diuretics, such as triamterene, to avoid hypokalemia.

### **Hormone replacement therapy**

Hypogonadism, whether or not secondary to corticosteroid therapy, should be considered in patients with osteoporosis. Estrogen with or without progesterone therapy was associated with an increase in lumbar spine bone density in 15 women with asthma treated with oral prednisone.<sup>48</sup> Similar results have been reported in 42 subjects with rheumatoid arthritis treated with corticosteroids.<sup>49</sup> Therefore postmenopausal women receiving inhaled or systemic corticosteroids should receive hormone replacement therapy if there are no contraindications for such therapy. Premenopausal women who experience menstrual irregularities while receiving inhaled or systemic corticosteroids may benefit from oral contraceptive therapy or cycling with estrogen and progesterone. Asymptomatic, corticosteroid-treated women with reduced serum levels of estradiol or increased follicle-stimulating hormone also may benefit from hormone replacement or supplementation.

Testosterone deficiency is a recognized cause of osteoporosis, and therefore corticosteroid-treated men may benefit from testosterone replacement if serum testosterone levels are low. Testosterone replacement resulted in improvement in bone density in a small number of men with low serum testosterone levels and asthma.<sup>50</sup> Lumbar, but not hip, bone density increased in these subjects. It is reasonable to consider testosterone replacement for subjects with low serum testosterone levels who are receiving inhaled or systemic corticosteroids.

### **Bisphosphonates**

Bisphosphonates are pyrophosphate analogues that bind to hydroxyapatite at bone remodeling sites and inhibit bone resorption. They have a long half-life and sustained inhibition of bone resorption. There are 3 bisphosphonates available in the United States: etidronate (Didronel), pamidronate (Aredia), and alendronate (Fosamax). Pamidronate is only available for intravenous

**TABLE IV.** Summary of risk assessment

| Risk                                                                                                       | Recommendations                                                                                                                                                                                                                             |
|------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Low                                                                                                        |                                                                                                                                                                                                                                             |
| Adult: $\leq 800$ $\mu$ g BDP;<br>child: $\leq 400$ $\mu$ g BDP*                                           | Adequate calcium, vitamin D;<br>weight-bearing exercise;<br>no tobacco, limited alcohol;<br>check TSH in patient with<br>history of thyroid<br>abnormality                                                                                  |
| Medium                                                                                                     |                                                                                                                                                                                                                                             |
| Adult: $> 800$ $\mu$ g BDP;<br>child: $> 400$ $\mu$ g BDP*                                                 | As above plus<br>measure height annually;<br>consider estrogen in post-<br>menopausal women without<br>contraindications; consider<br>DXA if inhaled steroid dose<br>$> 1200$ $\mu$ g/day for adults or<br>$> 600$ $\mu$ g/day for children |
| High                                                                                                       |                                                                                                                                                                                                                                             |
| Chronic systemic CS or<br>systemic CS for $> 4$ contin-<br>uous weeks, or more than<br>4 7-day bursts/year | As above plus<br>24-hr urine for calcium and<br>creatinine for those on<br>chronic CS; DXA; measure<br>free testosterone in men and<br>consider replacement<br>therapy if low                                                               |

CS, corticosteroid.

\*BDP or BDP equivalent. Add nasal corticosteroid dose to other inhaled steroid dose.

administration. Etidronate has been shown to be effective in the primary prevention of osteoporosis resulting from systemic corticosteroid therapy (simultaneous initiation of etidronate and corticosteroid therapy).<sup>51</sup> Both etidronate and pamidronate are effective for the treatment of osteoporosis caused by systemic corticosteroid therapy.<sup>52</sup> Trials of alendronate in secondary prevention are in progress. Preliminary results show the bone mineral density of the vertebrae increased by 2.78% and that of the femoral neck increased by 0.22% in patients treated with alendronate (10 mg/day) while receiving prednisone (10 mg/day).<sup>53</sup> Etidronate is not taken daily but is *cycled* for 2 weeks every 13 weeks. Adults receive 400 mg/day. Two small studies of postmenopausal women treated with systemic corticosteroids, one for temporal arteritis and the other for rheumatoid disease and asthma, showed increases in lumbar spine bone density with etidronate plus calcium therapy.<sup>54,55</sup> The second study showed an increase in bone density in the femoral neck, with beneficial effects sustained at 24 months. Two studies of etidronate and one with pamidronate (150 mg/day) demonstrated an increase in bone density when treatment was initiated after systemic corticosteroid therapy.<sup>56</sup> Etidronate was administered intravenously every 3 months. Intravenous alendronate has prevented bone loss in corticosteroid-treated girls with chronic rheumatic disease. In summary, bisphosphonates show promise for the treatment and prevention of corticosteroid-induced osteoporosis.

Bisphosphonates are retained long-term in the skeleton, and thus caution should be exercised in treating younger patients. Oral alendronate has been associated with esophageal irritation and strictures, but it is usually tolerated when taken with at least 6 ounces of water 30 minutes before ingestion of the first food or beverage of the day.<sup>57</sup> Oral bisphosphonate therapy should be used cautiously in patients with swallowing disorders.

## Calcitonin

Calcitonin is approved for the treatment of osteoporosis and inhibits bone resorption by its direct effect on osteoclasts. The therapy is administered subcutaneously (100 IU/day or every other day) or intranasally (200 IU/day). Resistance may develop to calcitonin therapy after 18 months because calcitonin antibodies inhibit its action. Calcitonin may rapidly decrease bone pain caused by osteoporotic fracture. It has also been shown to be useful for the treatment and prevention of bone loss. Calcitonin improved vertebral and forearm bone mass during a 1-year study of adults with asthma treated with glucocorticoids (mean dosage, 10.9 mg prednisone/day).<sup>27,58</sup> Calcitonin was ineffective in preventing bone loss in another study of corticosteroid treatment of polymyalgia rheumatica. Thus the role of calcitonin in corticosteroid-induced osteoporosis is less certain than that for bisphosphonates. Nevertheless, calcitonin therapy may be useful in children and in adults with contraindications to hormonal replacement and bisphosphonates.

## Potential new medications

Agents under investigation include intermittent parathyroid hormone administration and selective estrogen receptor modulators (eg, raloxifene [Evista] and tamoxifen).<sup>2,59,60</sup> Raloxifene decreases bone resorption and increases bone mineral density in the lumbar spine in postmenopausal women without stimulating endometrial growth.<sup>59,60,61</sup> Raloxifene may provide a replacement for estrogen for those women who cannot or prefer not to use estrogen after menopause.

## RECOMMENDATIONS

Allergist-immunologists evaluate and treat patients of all ages. The prevalence of osteoporosis will increase with the aging of the population. Therefore allergist-immunologists should counsel their patients concerning osteoporosis. The following are recommendations made on the basis of available medical literature review and a consensus of members of the panel (Table IV).

### Low risk

Subjects treated with inhaled corticosteroid dosages of no more than 800  $\mu$ g/day BDP or the equivalent for adults or no more than 400  $\mu$ g/day BDP or the equivalent for children have a risk of osteoporosis similar to that of the general population. Nasal corticosteroid doses should be added to the amount used to treat asthma for total corticosteroid load for both adults and children.

1. Maintain adequate calcium intake. *Calcium intake is critical during the growing years, especially in adolescence when bone growth is maximal.*<sup>62</sup> Calcium supplementation or increased dietary calcium is important if milk and dairy products are to be avoided, such as with food allergy or intolerance. Detailed recommendations for patients can be found in "Boning Up on Osteoporosis, A Guide to Prevention and Treatment" (National Osteoporosis Foundation, 2100 M Street, M.W. Suite 602 Washington, DC 20037. Telephone: [202] 223-2226).
2. Encourage exercise, particularly weight-bearing exercise. *Specific exercise recommendations are available in "Boning Up on Osteoporosis" (see above).*
3. Supplement diet with vitamin D, particularly if sun light exposure is limited. *Although vitamin D is found in egg yolks, salt-water fish, liver, and vitamin D-fortified milk, milk is the only significant dietary source, and not drinking milk is a risk factor for osteoporosis. Individuals who have a chronic disease may have a greater need for vitamin D than normal subjects.*
4. Discourage cigarette smoking and excessive ethanol ingestion.
5. Ensure euthyroid status by thyroid-stimulating hormone (TSH) measurement for patients on thyroid supplementation.
6. Use the lowest effective corticosteroid dose and/or topical preparations whenever possible. *As recommended by the 1997 National Heart, Lung, and Blood Institute Guidelines,<sup>1</sup> always try to lower the corticosteroid dosage when therapeutic goals have been met.*

### Moderate risk

Subjects treated for more than 6 weeks with more than 800 µg/day inhaled BDP or the equivalent for adults or more than 400 µg/day BDP or the equivalent for children have an increased potential risk of osteoporosis. Nasal corticosteroid dosages should be added to the amount used to treat asthma for total corticosteroid load for both adults and children.

1. Follow low-risk recommendations. *Review calcium and vitamin D intake and other risk factors (Table I).*
2. Measure height annually. *Asymptomatic vertebral compression fractures are common in subjects with osteoporosis. If an adult loses more than 1 inch of height, bone densitometry is recommended. A lateral thoracolumbar spine radiograph should be considered to evaluate compression fractures. If either study is abnormal, further evaluation is suggested. Children or adolescents whose growth rate declines are a special concern. Evaluation for causes of growth delay and review of asthma therapy, particularly corticosteroid therapy, should occur. A bone densitometry may be indicated.*
3. Consider estrogen replacement therapy for postmenopausal women without identified contraindications.
4. Consider bone densitometry.

### High risk

Subjects who are treated with chronic systemic corticosteroid therapy or systemic therapy for more than 4 contiguous weeks or who receive more than 4 7-day bursts of systemic corticosteroids per year have an increased risk of osteoporosis.

1. Follow low-risk recommendations. *Review calcium and vitamin D intake and other risk factors (Table I).*
2. Obtain 24-hour urine collection for calcium and creatinine for individuals receiving chronic systemic therapy.
3. Assess bone density. *If the T score is decreased more than one standard deviation below the mean, then initiate evaluation and treatment or refer to an authority in osteoporosis management.*

### EVALUATION

Evaluation may include measurement of serum calcium, creatinine, phosphorous, alkaline phosphatase, liver transaminases, TSH, level of estradiol in premenopausal women with change in their menstrual cycle, free testosterone in males, and 24-hour urine for calcium and creatinine. Additional studies considered by osteoporosis specialists include 25-OH vitamin D serum level in select cases (eg, malabsorption, poor dietary intake, or chronic liver disease) and parathyroid hormone levels for hypercalcemia.

### Treatment

Treatment includes the following:

- Estrogen replacement therapy for women without contraindication for such therapy who are postmenopausal or with hypogonadal function and evaluation for estrogen replacement therapy (including breast exam, pelvic exam, and mammography) should be considered.

### OR

- Testosterone therapy for men with low free testosterone levels should be considered (pretreatment evaluation should include a digital examination of the prostate and a prostate-specific antigen level).

### AND

- Oral bisphosphonate or calcitonin is recommended for osteoporosis. *The bisphosphonates available are cyclic etidronate (400 mg/day) for 2 weeks every 3 months or oral alendronate (10 mg/day). Oral calcium supplements should be discontinued on days of etidronate therapy. Alendronate is administered 1 hour before meals or 2 hours after meals to enhance absorption. Alendronate ideally should be swallowed with 8 ounces of water or more, and the recipient should remain upright for 1 hour after administration to minimize the possibility of esophageal ulceration. Evaluation of suspected swallowing disorders may be necessary*

*before alendronate therapy. Alendronate may be difficult to administer if there are any swallowing difficulties. Calcitonin (200 IU/day) by nasal spray or by subcutaneous injection (100 IU/day) is an alternative therapy. Nasal calcitonin may be mildly irritating to the nasal mucosa.*

## AND

- Thiazide combined with amiloride should be considered if the 24-hour urine calcium is more than 300 mg/24 hrs or if there is a history of ureterolithiasis. Serum potassium should be monitored.

Additional assessments, such as bone biopsy or additional treatment with low dose parathyroid hormone, testosterone, growth hormone, fluoride therapy, high dose vitamin D (greater than 800 U/day) or 1,25 (OH)<sub>2</sub>-vitamin D, should be supervised by a bone disease specialist.

## A SPECIAL CONSIDERATION: CHILDREN AND ADOLESCENTS

Long-term use of systemic corticosteroids is associated with osteoporosis in younger age groups.<sup>63,64</sup> Furthermore, corticosteroid use in these age groups may result in failure to achieve peak bone mass, a risk for osteoporosis later in life.<sup>65-68</sup> Although alternate-day morning dosing of prednisone does not appear to protect against osteoporosis for any age group, in children such dosing is more likely to preserve normal linear growth.<sup>69</sup> Whether the long-term use of inhaled steroids causes osteoporosis remains an area for study.<sup>70-75</sup>

Factors that enhance attainment of optimal peak bone mass include increased physical activity, weight, strength or muscle mass, calcium intake, general nutrition, and hormonal status.<sup>76-79</sup> As noted earlier, any disorder resulting in estrogen deficiency or testosterone deficiency is associated with osteoporosis. In adolescents, estrogen deficiency may occur with anorexia nervosa.<sup>80-82</sup> Hypothalamic amenorrhea may result from vigorous athletic activity.<sup>83,84</sup> Resultant estrogen deficiency diminishes bone accretion despite the fact that mechanical stress on bones from activity usually enhances bone accretion. Furthermore, children whose parents have low bone density may also be at higher risk for osteoporosis because up to 75% of peak bone density is genetically determined.<sup>82</sup>

Bone density may be assessed in children as it is in adults.<sup>76,77,85,86</sup> DXA bone densitometer readings for children as young as 5 years of age are interpreted according to available childhood standards. For younger ages, a hand film may be used for screening purposes. In addition to the recommendations listed in the preceding paragraphs, a bone density test should be performed for a moderate or high risk patient who "falls off the growth curve" because decreased linear growth is likely to be associated with decreased bone accretion.

Treatment beyond assuring adequate calcium and vitamin D intake has not been established for children. In a patient with amenorrhea at moderate-to-high risk of

osteoporosis, estrogen therapy may be considered. Most bone experts are reluctant to use sodium fluoride or bisphosphonates because of the possible long-term effects of incorporation of these agents into the maturing skeleton. Calcitonin has been used and appears relatively safe, at least in the short term, in the severely osteoporotic child and may provide some analgesia for acute fractures and chronic bone pain. Consulting a pediatric endocrinologist with an interest in osteoporosis may be helpful at this point.

## NEEDS

Many questions remain to be answered for the diagnosis, monitoring, and treatment of glucocorticoid-induced osteoporosis. Recommendations to help answer these questions include the following:

- Additional long-term, large population data to determine whether a threshold dosage exists below which inhaled corticosteroids will not result in significant bone loss, regardless of the duration of therapy. *These data are difficult to obtain because of extenuating effects of intermittent systemic corticosteroid therapy, variability in dosage of corticosteroid used for asthma therapy, various types of inhaled corticosteroids for which therapeutic and adverse reaction comparisons are not available, different inhalational delivery systems, intersubject variability in sensitivity to the effects of corticosteroids, and difficulties in assessing adherence to prescribed regimens.*
- Development of more cost-effective and better screening or monitoring tests that might identify at-risk subjects or verify rapid responses to therapy.
- Development of medications that enhance bone formation because current therapies primarily affect resorption.
- Increased awareness that osteoporosis can occur with asthma and that calcium intake, adequate vitamin D, and exercise minimize this risk.
- Optimal use of existing therapies for asthma that do not affect or have the potential to affect bone metabolism. *These include environmental control measures, immunotherapy, theophylline, and non-corticosteroid antiinflammatory agents such as cromolyn, nedocromil, and leukotriene modifiers. Aggravating conditions, such as sinusitis and gastrointestinal reflux, should also be treated.*
- Development of new asthma therapies that do not affect or have the potential to affect bone metabolism.
- Additional studies of the influence of inhaled corticosteroid therapy during the years when peak bone mass is achieved.
- Better definition of the fracture threshold for subjects treated with corticosteroids.
- Determine the value, if any, of pharmacologic prevention of osteoporosis in patients receiving long-term high-dose inhaled glucocorticoids.

## CONCLUSION

It is important that physicians using corticosteroid therapy for subjects with asthma be aware of risk factors for osteoporosis, initiate timely diagnostic studies or referrals to rule out this disease, and when present institute appropriate therapy or referrals.

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