
CME review article

This educational activity is supported by an educational grant from GlaxoSmithKline.

The effects of corticosteroids on bone growth and bone density

David Weldon, MD

Objective: To define the effects of both parenteral and inhaled corticosteroids on bone growth in children and the development of osteopenia and osteoporosis in children and adults.

Data Resources: Articles in PubMed and MEDLINE published from 1983 to 2008 were searched. Keywords used included *corticosteroids and bone growth, osteopenia, osteoporosis, and bisphosphonates*.

Study Selection: Publications reviewed include randomized, placebo-controlled studies of both children and adults.

Results: Because systemic and high-dose inhaled corticosteroids affect bone growth of children taking these medications, stadiometry should be used to measure the growth of children. Osteoporosis due to repetitive courses of oral or parenteral corticosteroids and inhaled corticosteroids can develop gradually in the aging adult. Prophylaxis against osteoporosis requires an index of suspicion, assessment of bone density, supplemental calcium and vitamin D, and use of bisphosphonates to prevent bone fractures that could compromise the patient's quality of life.

Conclusion: Preventing corticosteroid-induced effects on bone metabolism can allow effective treatment of allergic disease without long-term adverse effects.

Ann Allergy Asthma Immunol. 2009;103:3–11.

Off-label disclosure: Dr Weldon has indicated that this article does not include the discussion of unapproved/investigative use of a commercial product/device.

Financial disclosure: Dr Weldon has indicated that in the last 12 months he has not had any financial relationship, affiliation, or arrangement with any corporate sponsors or commercial entities that provide financial support, education grants, honoraria, or research support or involvement as a consultant, speaker's bureau member, or major stock shareholder whose products are prominently featured either in this article or with the groups who provide general financial support for this CME program.

Instructions for CME credit

1. Read the CME review article in this issue carefully and complete the activity by answering the self-assessment examination questions on the form on page 12.
2. To receive CME credit, complete the entire form and submit it to the ACAAI office within 1 year after receipt of this issue of the *Annals*.

INTRODUCTION

Several studies have indicated that corticosteroids are not without the potential for long-term adverse effects on bone metabolism, growth, and strength. Inhaled corticosteroids, although safer, may produce adverse effects on bone metabolism. The purpose of this review is to define the risk factors for and treatments that may prevent growth suppression in children and osteopenia and/or osteoporosis in children and adults.

GROWTH SUPPRESSION IN CHILDREN

A variety of factors play a role in the proper interpretation of a child's growth pattern, especially genetics (ie, a constitutional delay may result in a slower growth phase initially

before a normal phase ensues). According to Allen,¹ there are 3 phases of childhood growth: nutrition-dependent growth of infancy (the fastest growth phase), the growth hormone-dependent linear second phase from infancy to prepuberty, and the pubertal phase, which ends with epiphyseal growth plate maturation. Glucocorticoids enhance hypothalamic somatostatin secretion, which inhibits pulsatile pituitary growth hormone secretion. Glucocorticoids also downregulate the expression of growth hormone receptors and their binding activity.² Insulinlike growth factor 1 (IGF-1) is also decreased by decreasing circulating protein binding of IGF-1 in children treated with glucocorticoids.³

EFFECT OF SYSTEMIC CORTICOSTEROIDS ON GROWTH

How corticosteroids affect a child's growth varies, however, based on the underlying disease process and the timing of administration of the corticosteroids. Compared with children

Affiliations: Department of Internal Medicine, Texas A&M University Health Sciences Center, College Station, Texas.

Received for publication April 30, 2009; Received in revised form May 26, 2009; Accepted for publication May 28, 2009.

with simple obesity, children with Cushing disease had greater decreases in height (mean [SD], -1.88 [0.24] in those with Cushing disease compared with 1.18 [0.19] in those with obesity; $P < .05$) and in body mass index compared with height (mean [SD], -1.81 [0.54] compared with 0.9 [1.17] for those with Cushing disease vs obesity; $P < .0001$).⁴ Premature children whose mothers were administered 2 doses of betamethasone antenatally had no significant effect on bone density measurements or adult height (when measured as adults) compared with mothers who were given placebo.⁵ Infants administered oral prednisone at 2 mg/kg daily in divided dosages for 3 months followed by tapering for more than 6 to 9 months had greater growth suppression as measured by height ($P < .001$) and weight ($P = .003$) at 1 year compared with infants administered a pulse dose of 30 mg/kg daily for 3 days (monthly) for 3 consecutive months.⁶

Knemometry has been used to measure growth velocity based on short-term measurements of the lower leg. However, knemometry is deemed "too sensitive" and does not reflect long-term growth of the child.⁷ For example, prednisolone at a dosage of 2.5 to 5 mg/d suppresses short-term lower leg growth as measured by knemometry.⁸ Children with Crohn disease who were treated with low-dose prednisone at a dose of 0.1 to 0.4 mg/kg daily for at least 8 weeks (mean of 14 months) were found to have growth suppression in 19% of patients who previously had normal growth velocity. Of those affected, only 31% had "catch up" growth, with those more likely to recover their anticipated height within 1 year if they had reached the age of expected age peak height velocity (12.5 years for girls and 13.5 years for boys).⁹ In children with severe asthma who required intermittent, alternate-day, or daily oral corticosteroids along with high dose (mean [SD], $1,675$ [94] $\mu\text{g/d}$) maintenance inhaled corticosteroids, significant decreases in growth were noted compared with their peers (SDs, -0.44 , -1.22 , and -0.93 for intermittent, alternate day, and daily corticosteroid use, respectively). Individuals requiring more than 10 mg of prednisone on alternate days had greater growth suppression (SD, -1.55) compared with those who required less than 10 mg

(SD, -0.41 ; $P < .03$). Those children who had more than -1 SD of growth were more likely steroid dependent for longer periods (51.2 vs 27.5 months, $P < .003$).¹⁰

Table 1 summarizes evaluations of inhaled corticosteroids and growth suppression in children. One meta-analysis revealed that medium-dose inhaled corticosteroids reduced linear growth velocity by 1.51 cm/y for beclomethasone dipropionate and 0.43 cm/y for fluticasone.¹⁸ Compared with beclomethasone dipropionate and chlorofluorocarbon, the dosing of beclomethasone dipropionate and hydrofluoroalkane is halved but the effect is comparable in decreasing the stadiometer-measured height velocity directly proportional to the comparable dose of beclomethasone dipropionate and chlorofluorocarbon.¹⁹ However, when used at the recommended dosages of 100 to 200 $\mu\text{g/d}$ of beclomethasone dipropionate and hydrofluoroalkane or 200 to 400 μg of beclomethasone dipropionate chlorofluorocarbon (with volumetric spacer), no significant differences were found in growth velocities (5.27 vs 5.71 cm/y, $P = .129$). Ciclesonide (160 $\mu\text{g/d}$) demonstrated minimal growth suppression (-0.15 cm/y) with stadiometer measurements of prepubertal children with asthma.¹³ Long-term studies with budesonide showed a transient slowing of growth in the first year of use but no significant effect on final attained adult height.^{17,20} A more pronounced reduction in growth was seen in younger children and in children with pretreatment lower relative heights.²⁰ Although most studies¹⁷⁻²⁰ documented slowing of growth in the early stages of long-term inhaled corticosteroid use, the good news is that no matter what the inhaled corticosteroid study reveals, children will attain their anticipated height as adults.²¹

EFFECTS OF SYSTEMIC CORTICOSTEROIDS ON BONE DENSITY IN CHILDREN

In children, lumbar bone mineral density (BMD) scores adjusted for age- and sex-specific variations (z score) revealed that females were more likely to have osteopenia than males (mean [SD], -1.06 [0.13] and -0.78 [0.16], respectively). In that study, 55% of females (compared with 35% of males)

Table 1. Review of Studies on Inhaled Corticosteroids on Growth of Children

Source	Year	ICS	Dose	Result(s)
Skoner et al ¹¹	2000	Beclomethasone dipropionate	168 μg twice daily	-0.9 cm
Schenkel et al ¹²	2000	Mometasone	100 μg daily	NS change
Skoner et al ¹³	2008	Ciclesonide	40 $\mu\text{g/d}$	-0.15 cm/y
Pauwels et al ¹⁴	2004	Budesonide	200 $\mu\text{g/d}$ DPI	-0.58 cm at year 1, -0.43 cm at year 2, and -0.33 cm at year 3
Allen et al ¹⁵	1998	Fluticasone	100 $\mu\text{g/d}$ DPI	NS change
Ferguson et al ¹⁶	1999	Fluticasone	400 $\mu\text{g/d}$ DPI	Budesonide, 6.2 mm
		Budesonide	800 $\mu\text{g/d}$ DPI	Less than fluticasone at 20 weeks
CAMP study ¹⁷	2000	Budesonide	200 $\mu\text{g/d}$ DPI	-1.1 cm (year 1)
Pedersen ¹⁹	2002	Beclomethasone dipropionate	<200 $\mu\text{g/d}$ HFA	NS change
Agertoft ²⁰	2000	Budesonide	412 mcg/day DPI	-1 cm (year 1 only)

Abbreviations: CAMP, Childhood Asthma Management Program; DPI, dry powder inhaler; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; NS, nonsignificant.

were likely to have a z score of -1 or less. In children who were glucocorticoid dependent, z scores increased from -0.7 [0.13] for those taking intermittent oral corticosteroids, -0.98 [0.23] for those taking daily corticosteroids, and, surprisingly, -1.26 [0.2] for those taking alternate-day oral corticosteroids. Likewise, children with osteoporosis (z score of -2 or less) had similar percentages dependent on the dosing interval of oral corticosteroids (10%, 13%, and 30%, respectively; $P < .02$). Children who received 10 mg or more of prednisone every other day were at greater risk of developing osteopenia (69%) compared with those taking less than 10 mg every other day (21%, $P < .003$). Growth suppression in these children was highly associated with osteopenia (odds ratio [OR], 5.6; 95% confidence interval, 2.7–11.8; $P < .0001$).¹⁰

OSTEOPENIA AND OSTEOPOROSIS

Osteopenia is a condition characterized by decreased bone mass and a predecessor of osteoporosis. Osteoporosis is defined by lower bone mass with deterioration of bone tissue. Both mineral and matrix loss are proportionately lost with a result in decreased bone strength and increased risk of fractures. As a patient ages, bone resorption exceeds bone formation with peak strength of cortical bone between 30 and 35 years of age and trabecular strength starting to decline after the age of 35 years.²² The annual loss of trabecular bone is linear, with a rate of up to 1.2% for men and upward of 4% for women after the age of 35 years. Postmenopausal women may lose up to 10% per year up to 7 years after menopause.²³ Table 2 defines risk factors for osteoporosis. Genetics also

play a vital role in the developing osteoporosis, with increased risk seen in patients with polymorphism of an Sp-1 cleavage site of the first intron of the collagen gene and genes affecting estrogen receptor, transforming growth factor β (TGF- β), apolipoprotein E, bone morphogenetic protein 2, and low-density lipoprotein receptor-related protein 5.

Estrogen deficiency is a noted risk factor for postmenopausal women but is also seen in older men. Men with a deficiency in aromatase (which converts testosterone to estrogen) have increased incidence of osteoporosis, and estrogen therapy helps to reverse this trend.²⁴ Successful testosterone supplementation in preventing osteoporosis in men at risk appears to be related to the estrogen concentration.²⁵ Estrogen increases the release of TGF- β from osteoblasts in vitro, and the combination appears important in promoting osteoclast apoptosis.²⁶ Tumor necrosis factor from mononuclear cells increases osteoclast recruitment and its release is inhibited by estrogen.²⁷ Interleukin 1 (IL-1) is a potent stimulator of bone resorption, and the decoy receptor for IL-1 (IL-1R2), which binds IL-1 and prevents its action on the IL-1 cellular receptors, is increased by estrogen.²⁸

IL-6, via a prostaglandin-mediated mechanism, promotes osteoclast production and bone resorption.²⁹ Interestingly, cyclooxygenase 2 inhibitors have demonstrated different results in BMD studies of men (-3.1%) and women ($+3\%$) at the hip.³⁰ Interestingly, both IL-4 and IL-13 interfere with cyclooxygenase 2-mediated prostaglandin synthesis in osteoblasts and thus decrease bone resorption.³¹ Osteoclasts are activated by colony-stimulating factor 1, and IL-18 produced by osteoblasts works in conjunction with granulocyte-monocyte colony-stimulating factor to reduce osteoclast activity.³²

Table 2. Osteoporosis Risk Factors

Primary causes
Sex (female > male)
Race (white, Asian > Hispanic > African American)
Previous family history
Sedentary lifestyle/immobilization
Reduced calcium intake childhood or adolescence
Amenorrhea/hyperprolactinemia/panhypopituitarism
Natural or surgical menopause
Hypogonadism/Turner and Klinefelter syndrome/Marfan syndrome
Low body weight or bone mass/thinness/small stature/anorexia
Cystic fibrosis/homocystinuria/osteogenesis imperfecta/Gaucher disease
Hyperparathyroidism/hypophosphatemia
Celiac disease (gluten sensitive enteropathy)
Secondary causes
Cigarette smoking (passive or active)
High caffeine intake/high salt intake/low calcium intake
Vitamin D deficiency (intake or malabsorption)
Alcohol use (3 drinks per day or more)
Medications (corticosteroids, cyclosporine, warfarin or heparin, phenytoin)
Excessive thyroid supplementation
Inflammatory diseases (rheumatologic)
Mastocytosis

MEASUREMENT OF BONE DENSITY

Techniques available for measuring BMD vary. Cortical bone of the forearm (which has a slower turnover compared with trabecular bone) can be measured by single-photon absorptiometry. Cortical and trabecular bone is usually evaluated with dual x-ray absorptiometry (DXA). Scoring of BMD is based on either T scores (the number of SDs above or below the average BMD for a young healthy white woman) or z scores (the number of SDs above or below the average BMD for age- and sex-matched controls). The z scores are important in defining lifetime risks of osteoporotic fracture, with 1.5- to 3-fold increases in fracture for each SD decrease in bone density.³³ Osteoporosis is defined as a T score less than -2.5 SDs, whereas osteopenia is defined as between -2.5 and -1.0 SDs. Factors that may affect the accuracy of DXA scanning include taking calcium supplements within 24 hours of scanning and anatomical changes of the axial skeleton (eg, compression fractures, scoliosis, osteophytes, and laminectomy).³³

Alternative indicators of bone metabolism and turnover, such as procollagen and osteocalcin, were not useful in a study of elderly (mean [SD] age, 60.7 [12.6] years) asthmatic patients compared with DXA scans. Although lower 8 AM cortisol levels were associated with worse T scores of the

spine ($P = .003$), high false-positive (26%) and false-negative (31%) rates limited its usefulness. For hip measurements, lower morning cortisol levels were slightly better in predicting decreases in T scores (13% false positive and 21% false negative). However, these levels, longer prednisone exposure, lower current dosing of prednisone, older age, and inhaled steroid dosage were not useful in defining those who required diagnostic densitometry.³⁴ Bone loss due to corticosteroids is greater in trabecular bone (vertebral bodies, femoral heads, proximal humeri, distal radii, and ribs) compared with cortical bone. The greatest risk for bone loss occurs within the first 6 to 12 months of systemic corticosteroid use, with prednisone at 25 mg every other day causing 3.5% and 50 mg every other day causing a 17% reduction in trabecular bone loss in 1 year.³⁵

EFFECT OF INHALED CORTICOSTEROIDS ON BONE DENSITY

The data are more encouraging for patients with bone loss taking inhaled corticosteroids (compared with oral corticosteroids), but inhaled corticosteroids are not totally without risk. In a regression analysis of lumbar BMD z scores on the daily dose of inhaled corticosteroid in patients who had used oral prednisone for a mean (SD) of 10.7 (9.7) years, the lumbar BMD z score decreased by 0.5 SD for each 1-mg increment in the daily dose of inhaled steroid, with most patients (71%) taking inhaled budesonide for more than 10 years. However, larger lifetime inhaled corticosteroid use (especially in sparing the use of oral corticosteroids) was associated with more normal lumbar BMD z values ($P = .002$) and a reduction of patients at risk of fracture.³⁶ Premenopausal women taking inhaled triamcinolone were found to have (more than 3 years) a slight decrease in bone density measured at the trochanter and hip of 0.00044 g/cm² per 100 μ g/d of triamcinolone per year of treatment, and with high-dose triamcinolone (1,200 μ g/d), a woman's risk for hip fracture doubles.³⁷ Likewise, in a double-blind, placebo-controlled trial of older patients (mean [SD] age, 55.7 [6.9] years), triamcinolone, 600 μ g twice daily, after 3 years decreased the BMD of the femoral neck by 1.78% more with inhaled triamcinolone compared with placebo ($P < .001$). Although the BMD of the lumbar spine increased by almost 1% in the placebo group, it decreased by 0.35% in the inhaled corticosteroid group ($P = .007$).³⁸ However, inhaled fluticasone propionate powder, 500 μ g twice daily, for up to 2 years did not affect either the hypothalamic-pituitary-adrenal axis or BMD.³⁹

An increased risk of hip fracture in patients taking inhaled corticosteroids (dose dependent) was noted in a large cross-sectional study in the United Kingdom, with an OR of 1.19 (after adjusting for use of oral corticosteroids). An almost linear relationship in ORs was noted with the lowest risk at less than 200 μ g/d (OR, 1.1) to an OR of 1.5 for patients taking 801 to 1,600 μ g/d and then increased exponentially to an OR of 2 for those taking more than 1,601 μ g/d.⁴⁰ In Canada, a similar case-controlled study found that the risk of

hip or upper limb fracture increased significantly by 12% for each 1,000- μ g/d ($>1,000$ μ g) dose of inhaled corticosteroid.⁴¹ Finally, in 1 study, adrenal suppression from high dosages of ICSs (range, 800–2,000 μ g/d for a mean of 24 months, either beclomethasone dipropionate or budesonide), correlated with decreased bone density when compared with body mass index.⁴²

Although many of this data implicate high-dose ICS in decreasing BMD, a mathematical simulation model using low-dose ICSs for 10 years justified the use of ICSs in the management of asthma with minimal increases in costs attributable to hip fracture.⁴³ Thus, the prudent recommendation in the management of asthmatic patients and those requiring nasal or topical corticosteroids is to use the lowest dose that controls the condition without the use of oral corticosteroids. A consideration in achieving this would be to use combined therapy with lower dosages of inhaled corticosteroids for moderate to severe persistent asthmatic patients.

TREATMENT

The saying "An ounce of prevention is worth a pound of cure" certainly applies to the use of systemic corticosteroids in the management of allergic disease. The use of a stadiometer is worthwhile and recommended to determine the growth rate of children. Measuring the height at 4-month intervals and comparing the slope of the points on a regression line are recommended. In an extensive review and comparison of inhaled corticosteroids, beclomethasone dipropionate appeared to have greater effect on suppression of growth in children compared with budesonide and fluticasone (which were not significantly different from placebo when used at low to medium dosages).⁴⁴ Ciclesonide has been shown to have little effect on growth and growth velocity (-0.15 cm/y at 160 μ g/d for 1 year).¹³

In children who had received an average of 2.4 oral or parenteral corticosteroid bursts, the attained height in adulthood was 1.5 cm less than the final height achieved by those not treated with oral or parenteral corticosteroids. No significant differences were found in the type of oral corticosteroid used with the final height attained.²¹ Overall, a slight decrease in growth velocity of 0.5 to 1.5 cm (in the first year) can be expected in children using low- to medium-dose inhaled corticosteroids (budesonide or beclomethasone).⁴⁵ Correlating this with the potential for inhaled corticosteroids on adrenal axis function, inhaled (especially when combined with intranasal) corticosteroids with higher bioavailability are more likely to induce transient effects on height velocity, and children taking these medications should be observed closely with stadiometry for the impact these medications have on their growth.⁴⁶

Osteopenia and osteoporosis are becoming more common as the average life span of patients becomes longer. Patients taking daily to alternate-day oral corticosteroids were at significant risk for fractures of the ribs and vertebrae, mostly reflected in decreases in trabecular bone mass.⁴⁷ Glucocorticoids decrease osteoblast function and increase the risk of

fracture of trabecular bone above that defined by bone densitometry. Osteocyte apoptosis has been proposed as 1 mechanism that enhances weakening of bone architecture. The effects of glucocorticoids can be seen as soon as the first 6 months of treatment, and thus preventive treatment should be considered for any patient receiving long-term corticosteroid therapy. This is especially true for all patients at risk for osteopenia and subsequent osteoporosis because of age and lack of gonadal hormones (eg, estrogen for women and testosterone for men).

A study documenting fracture rates in patients with asthma and/or chronic obstructive pulmonary disease defined a direct relationship with cumulative oral corticosteroid dosing and fracture risk. An almost logarithmic increase of life-time cumulative oral corticosteroids from 10 to 100 g of prednisolone increased the OR from 1 to 10, with fractures of the vertebra (OR, 10), femur (OR, 6), and ribs or sternum (OR, 3.2). Interestingly, other associated findings included bruising, weakness, height loss of more than 2.5 cm since the age of 25 years, cataracts, oral candidiasis, and “no teeth” all were individually significant ($P < .001$).⁴⁸ A meta-analysis of 6 studies revealed only a slight decrease (not significant) in BMD of 4.1%⁴⁹ with inhaled corticosteroids. In a study using high-dose inhaled corticosteroids (800 to 2,000 $\mu\text{g}/\text{d}$ of either beclomethasone or budesonide for a mean [SD] of 29.8 [19.5] months), a z score of -0.78 ($P = .0025$) compared with healthy age-matched controls revealed a mild decrease in femoral neck density.⁴²

TREATMENT OF CORTICOSTEROID-INDUCED BONE CHANGES

Laboratory and densitometry recommendations for evaluation of patients at risk are defined in Table 3.⁵⁰ Because glucocorticoids decrease intestinal calcium absorption and increase urinary calcium excretion, supplementation with a minimum of 1,000 to 1,500 mg/d of calcium and 800 IU/d of vitamin D is recommended. In patients receiving 5.6 mg/d of prednisone, prophylaxis with these supplements prevented a slight decrease in bone density in the lumbar spine and trochanter.⁵¹

HORMONE REPLACEMENT THERAPY

Whereas glucocorticoids reduce the production of sex hormones (estrogen, testosterone), supplemental therapy with estrogen in postmenopausal women taking oral corticosteroids resulted in improvement in bone density compared with those women who were not taking estrogen.⁵² However, because of increased risks of thromboembolism, breast cancer, and stroke, as well as disappointing results in coronary heart disease prevention, estrogen supplementation should be cautiously considered.⁵³ Raloxifene is a selective estrogen receptor modulator that significantly reduces the risk of breast cancer compared with estrogens and has no effect on the risk of cardiovascular disease or stroke. Whereas estrogen replacement therapy has shown beneficial effects on preventing both vertebral and nonvertebral fractures, raloxifene's

Table 3. Summary of Recommendations for the Prevention and Treatment of Osteoporosis as Proposed by the National Osteoporosis Foundation⁷²

Identify patients at risk (see Table 2)
Identify serum and urinary calcium excretion, serum (OH) 25 vitamin D level
Assess calcium and vitamin D intake
1,200 mg of calcium per day plus 800–1,000 IU of vitamin D daily recommended
Assess bone mineral density (DXA scan): hip and lumbar region better
Withhold calcium tablet on day of scan to exclude false elevation of density
Weight-bearing exercises, resistive exercises to improve muscle tone: daily
Assess falling risks: vision/hearing correction, neurologic problems, vertigo
Avoid smoking and alcohol abuse
Estimate patient's fracture risk during next 10 years (FRAX calculation) (www.shef.ac.uk/FRAX/)
For patients with DXA hip or spine T score ≤ -2.5 , previous vertebral or hip fracture, low bone mass with WHO risk factor of hip fracture $\geq 3\%$ or major osteoporosis-related fracture $\geq 20\%$, consider FDA-approved therapies:
Bisphosphonates
Calcitonin
Hormone replacement therapy
Parathyroid hormone (PTH 1–34, teriparatide)
Patients should be reassessed with laboratory and bone density every 2 years or when medically appropriate

Abbreviations: DXA, dual x-ray absorptiometry; FDA, Food and Drug Administration; WHO, World Health Organization.

effect has only been demonstrated for preventing vertebral fractures.⁵⁴ Tamoxifen is not indicated for osteoporosis prophylaxis. For men, the use of testosterone for those with testosterone deficiency (and no contraindications, such as prostate cancer) should be considered.

BISPHOSPHONATES

Bisphosphonates are analogues of pyrophosphate that bind to bone mineral and inhibit osteoclastic bone resorption. Treatment should be offered for those patients with bone densities at the lower range of normal for young adults (not for the expected normal for the age of the patient) who are starting long-term therapy with oral glucocorticoids.⁵⁵ Often, supplemental calcium is forgotten in the recommendations, and patients should be reminded of the importance to supplement their diet with at least 1,200 mg of calcium with 800 IU of vitamin D (unless they have calcium-related nephrolithiasis). The long-term consequences of bisphosphonate therapy in women of child-bearing age has not been defined. In a search of the MEDLINE and Embase databases (a retrospective analysis), no bone defects in infants born to mothers treated with bisphosphonates were found in 51 patients.⁵⁶ A prospective study of 21 women treated with bisphosphonates during or exposed to bisphosphonates of less than 3 months of pregnancy revealed no changes in fetal birth weight, gesta-

tional age, or birth defects compared with matched controls without bisphosphonate exposure.⁵⁷

Several studies have been published that document the effectiveness of bisphosphonates in the treatment of patients taking corticosteroids. Intermittent therapy with etidronate, 400 mg/d, for 2 weeks with calcium, 500 mg, for 76 days (each given for 4 cycles) was given to patients receiving high-dose oral corticosteroid therapy. Patients showed a mean (SD) improvement at 1 year of 0.61% (0.54%) in lumbar bone density and 1.46% (0.67%) in trochanter density with etidronate compared with a loss of 3.23% (0.6%) and 2.74% (0.66%), respectively, in patients with placebo.⁵⁸ In a study of patients taking low-dose prednisone, 8 mg/d, for greater than 6 months, patients taking low-dose elemental calcium (97 mg/d) plus vitamin D (400 IU/d) were shown to have had significant improvement in lumbar BMD with cyclical etidronate (400 mg/d for 2 weeks, repeated 8 times more than 2 years) compared with those only taking calcium and vitamin D (4.5% vs 1.65%, $P = .007$) during both 1- and 2-year measurements.⁵⁹

In a dose-dependent study of daily alendronate (2.5 mg, 5 mg, or 10 mg) vs placebo (all groups taking at least 800 mg of calcium plus 250 IU/d of vitamin D) in patients taking prednisone, 7.5 mg/d, a dose-dependent increase in BMD at the lumbar spine, trochanter, and femoral neck was seen for those taking 5 and 10 mg of alendronate (relative to placebo). The relative risk of fractures was less in the alendronate groups when compared with the placebo group (2.3% vs 3.7%).⁶⁰

In a comparison of alendronate, 10 mg/d, with calcium, 600 mg/d, vs calcium plus either vitamin D (ergocalciferol, 30,000 IU weekly) or calcitriol, 0.5 to 0.75 μ g/d, patients taking glucocorticoids were shown after 2 years to have a significant improvement in BMD of +5.9% with alendronate compared with the other 2 treatments. Six of the calcitriol patients had fractures compared with none of the alendronate patients at more than 2 years.⁶¹ Another study documented a more progressive decrease in BMD for patients taking oral prednisone of more than 7.5 mg/d for at least 12 months who had received placebo (loss of 3% at the lumbar spine, femoral neck, and femoral trochanter) compared with mild improvement for those taking risendronate, 5 mg/d, of 0.5% to 1% (relative to those taking 2.5 mg of risendronate). The overall fracture risk for patients taking 5 mg/d of risendronate compared with placebo was decreased (5.7% vs 17.3%, $P = .072$).⁶²

In a prospective study of Chinese patients using high-dose inhaled corticosteroid (beclomethasone or budesonide), patients inhaling 2 mg/d of ICS without supplement of calcium and/or intermittent etidronate had a BMD loss of between 1% (lumbar spine) and 2% (femoral neck) at 12 months. It was estimated that the average daily (baseline) calcium intake in all groups was 766 mg/d. Patients either receiving calcium supplementation of 1,000 mg or etidronate, 400 mg/d, for 14 days followed by calcium, 1,000 mg, for 76 days showed a modest increase in BMD at lumbar and trochanter of at least

2% for both calcium alone and calcium plus cyclical etidronate at 18 months and an increase of 1% for calcium alone (but not calcium plus etidronate) at the femoral neck.⁶³

Bisphosphonates approved for the treatment of corticosteroid-induced osteoporosis include alendronate (Fosamax), risendronate (Actonel), and zoledronic acid (Reclast). So far, only risendronate and zoledronic acid are approved for prevention. The dosing approved for alendronate and risendronate is daily (5 mg), which could lead to nonadherence because it must be taken on an empty stomach, upright, and at least 30 to 60 minutes before eating. Adverse effects of oral bisphosphonates include gastrointestinal upset, musculoskeletal pain, and, very rarely, atrial fibrillation. Zoledronic acid is given once a year as an infusion of 5 mg for more than 15 minutes. Although patients may consider yearly infusions for convenience, many patients may experience bone pain and fever within 3 days of the first infusion (improving with subsequent infusions). Despite this adverse effect, the HORIZON (Health Outcomes and Reduced Incidence with Zoledronic acid Once yearly) trial demonstrated that zoledronic acid, 5 mg, given once yearly was noninferior and superior to risendronate given at a dosage of 5 mg/d in the treatment of and prevention of glucocorticoid-induced osteoporosis at both the lumbar spine and femoral neck (seen 6 months and continuing for a further 6 months).⁶⁴ Osteonecrosis of the jaw related to bisphosphonates has been reported in patients receiving chemotherapy, dental extractions, and dental disease associated with osteomyelitis. Physicians should examine the dentition yearly for patients using bisphosphonates.

In a review of therapies for osteoporosis, MacLean et al⁶⁵ described several studies that compared risks of fractures caused by various agents. Bisphosphonates were superior compared with calcium supplementation alone, vitamin D supplementation, and hormone replacement therapy. Parathyroid hormone (PTH) replacement provided the best treatment for recovery of bone density. Although calcitonin is indicated for the treatment of postmenopausal osteoporosis, calcitonin failed to prevent or treat corticosteroid-induced fractures.⁶⁵ In another meta-analysis, calcitonin provided slight protection for corticosteroid-induced fractures due to osteoporosis in the vertebrae but not for nonvertebral fractures.⁶⁶

An encouraging aspect of bisphosphonates is that they continue to provide a decreased risk of fracture after their use is stopped. Alendronate has shown a stabilizing effect on BMD up to 5 years after long-term therapy.⁶⁷ As with the use of inhaled corticosteroids in patients with persistent asthma, stopping bisphosphonate therapy in patients who have osteoporosis will allow resumption of the deterioration but at a much slower rate compared with placebo.

PTH represents a therapeutic option for patients with osteoporosis and fractures who need more aggressive therapy to prevent future fractures. PTH prevents osteoblast apoptosis⁶⁸ and improves osteoblast density to enhance recovery of lost bone. Teriparatide (PTH 1–34) has been shown to have greater effect on bone recovery compared with alendronate (7.2 vs 3.4%, $P < .001$), especially with reducing the risk of

vertebral fractures ($P = .004$) and improving bone density in patients with glucocorticoid-induced osteoporosis.⁶⁹ Interestingly, although the combination of the 2 agents might be considered to have an additive effect in osteoporotic women, patients treated only with PTH had greater improvement in bone density.⁷⁰ Although there was no current benefit of using PTH with antiresorptive therapy concurrently, Grey and Reid⁷¹ recommended that using PTH first for 18 to 24 months and then switching to antiresorptive therapy would provide a better response in bone production and stability.⁷¹

RECOMMENDATIONS

The National Osteoporosis Foundation has recently issued an update on recommendations for the prevention and treatment of osteoporosis (www.nof.org).⁷² Table 3 summarizes some of the recommendations contained within this document. In a study of patients requiring 13.5 mg/d of prednisone for at least 1 year, calcium at 1,000 mg alone did not prevent bone loss (mean [SD], -4.3% [5.5%] in the lumbar spine) compared with those taking calcitriol with calcium or those with calcium, calcitriol, and intranasal calcitonin ($P = .0035$). However, no significant differences were found amid groups with loss of bone at the femoral neck.⁷³ Other studies^{60,61} have shown similar results with losses in the femoral neck with oral calcium alone in corticosteroid-dependent patients. In the study by Hanania et al.,⁴² patients treated in the long term with high-dose inhaled corticosteroids (average of $1,323 \mu\text{g/d}$) for 24 months (and in 4 of 18 patients enough inhaled corticosteroids to induce adrenal suppression) had decreases in bone density at the femoral neck (-0.78) when z scores were compared with those only taking bronchodilators. Patients with recurrent nasal polypsis responsive to oral corticosteroids (yet not due to aspirin hypersensitivity) and severe persistent asthma requiring oral corticosteroids may be the most likely candidates for consideration of prophylaxis with calcium, vitamin D, and a bisphosphonate.

A complete evaluation of the literature and conclusions regarding the cost-effectiveness of the use of bisphosphonates and other medications can be found at www.hta.ac.uk/full-mono/mon1107.pdf.⁶⁶ An algorithm was proposed by these authors based on a meta-analysis of the literature that recommended that patients 50 years and older who were receiving long-term corticosteroid therapy should be evaluated for risk of fracture. Patients taking 7.5 mg/d or more of oral corticosteroids are at greatest risk, but those who have had a fragility fracture are most likely to warrant therapy with bisphosphonates. Otherwise, the authors recommend evaluation of age and risk (eg, those <75 years of age with decreased BMD of -2 SDs can be treated, whereas those ≥ 75 years receive treatment without such assessments).⁶⁶ As inferred, older patients who have gonadal hormone deficiencies may require replacement, although the recommendations are more now appropriate for men without prostate cancer than women because of a slight risk of cancer and thromboembolism associated with hormone replacement therapies as defined in a recent Cochrane analysis.⁵³

CONCLUSION

Repetitive courses of oral corticosteroids and high-dose inhaled corticosteroids with higher bioavailability have significant effects on the bone growth of children. Likewise, osteopenia and osteoporosis can develop in older adults prescribed similar medications. Recognition of the potential for and surveying for risk factors of osteoporosis should be a consideration for all physicians who frequently treat patients with inflammatory diseases that require corticosteroids. Evaluation of daily calcium and vitamin D intake, height measured by stadiometry, and frequency of use of oral or parenteral corticosteroids should be considered for all patients at risk with each office visit.

REFERENCES

1. Allen DB. Inhaled corticosteroid therapy for asthma in preschool children: growth issues. *Pediatrics*. 2002;109:373–380.
2. Gabrielson BG, Carmignac DF, Flavell DM, Robinson IC. Steroid regulation of growth hormone (GH) receptor and GH-binding protein messenger ribonucleic acids in the rat. *Endocrinology*. 1995;136:209–217.
3. Hokken-Koelega AC, Stijnen T, DeMunick Keizerhyphen Schrama SM, et al. Levels of growth hormone, insulin-like growth factor-1 (IGF-1) and IL IGF-binding protein-1 and -3 and cortisol in prednisone-treated children with growth retardation after renal transplantation. *J Clin Endocrinol Meta*. 1993;77:932–938.
4. Greening JE, Storr HL, McKenzie SA, et al. Linear growth and body mass index in pediatric patients with Cushing's disease or simple obesity. *J Endocrinol Invest*. 2006;29:885–887.
5. Dalziel FR, Fenwick S, Cundy T, et al. Peak bone mass after antenatal betamethasone and prematurity: follow-up of a randomized control trial. *J Bone Miner Res*. 2006;21:1175–1186.
6. Pope E, Krafchik BR, Macarthur C, et al. Oral versus high dose pulse corticosteroids for problematic infantile hemangiomas: a randomized, controlled trial. *Pediatrics*. 2007;119:1239–1247.
7. Pedersen S. Assessing the effect of intranasal steroids on growth. *J Allergy Clin Immunol*. 2001;108:S40–44.
8. Wolthers OD, Pedersen S. Short-term linear growth in asthmatic children during treatment with prednisolone. *BMJ*. 1990;301:145–148.
9. Navarro FA, Hanauer SB, Kirschner BS. Effect of long-term low dose prednisone on height velocity and disease activity in pediatric and adolescent patients with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2007;45:312–318.
10. Covar RA, Leung DYM, McCormick D, et al. Risk factors associated with glucocorticoid-induced adverse effects in children with severe asthma. *J Allergy Clin Immunol*. 2000;106:651–659.
11. Skoner DP, Rachelefsky GS, Meltzer EO, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. *Pediatrics*. 2000;105:E23.
12. Schenkel EJ, Skoner DP, Bronsky EA, et al. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. *Pediatrics*. 2000;105:E22.
13. Skoner DP, Maspero J, Banerji D. Assessment of the long-term safety of inhaled ciclesonide on growth in children with asthma. *Pediatrics*. 2008;121:e1–e14.
14. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomized, double blind trial. *Lancet*. 2003;361:1071–1076.
15. Allen DB, Bronsky EA, LaForce CF, et al. Growth in asthmatic children treated with fluticasone. *J Pediatr*. 1998;132:472–477.
16. Ferguson AC, Spier S, Manjra A, et al. Efficacy and safety of high-dose inhaled steroids in children with asthma: a comparison of fluticasone propionate with budesonide. *J Pediatr*. 1999;134:422–427.
17. Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl*

- J Med.* 2000;343:1054–1063.
18. Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. *Pediatrics.* 2000;106:8–17.
 19. Pedersen S, Warner J, Wahn U, et al. Growth, systemic safety, and efficacy during 1 year of asthma treatment with different beclomethasone dipropionate formulations: An open-label, randomized comparison of extrafine and conventional aerosols in children. *Pediatrics.* 2002; 109:92–103.
 20. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med.* 2000;343:1064–1069.
 21. Silverstein MD, Yunginger JW, Reed CE, et al. Attained adult height after childhood asthma: effect of glucocorticoid therapy. *J Allergy Clin Immunol.* 1997;99:466–474.
 22. Ledford D, Apter A, Brenner A, et al. Osteoporosis in the corticosteroid-treated patient with asthma. *J Allergy Clin Immunol.* 1998;102:353–362.
 23. Scott JC. Epidemiology of osteoporosis. *J Clin Rheumatol.* 1997;3: S9–S13.
 24. Carani C, Qin K, Simoni M, et al. Effect of testosterone and estradiol in a man with aromatase deficiency. *N Engl J Med.* 1997;337:91–95.
 25. Falahati-Nini A, Riggs BL, Atkinson EJ, et al. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal and elderly men. *J Clin Invest.* 2000;106:1553–1560.
 26. Hughes DE, Dai A, Tiffie JC, et al. Estrogen promotes apoptosis of murine osteoclasts mediate by TGF-beta. *Nat Med.* 1996;2:1132–1136.
 27. Bismar H, Diel I, Ziegler R, Pfeilschifter J. Increased cytokine secretion by human bone marrow cells after menopause or discontinuation of estrogen replacement. *J Clin Endocrinol Metab.* 1995;80:3351–3355.
 28. Sunyer T, Lewis J, Osdoby P. Estrogen decreases the steady-state levels of the IL-1 signaling receptor (Type I) while increasing those of the IL-1 decoy receptor (Type II) mRNAs in human osteoclast-like cells. *J Bone Miner Res.* 1997;12:S135–140.
 29. Tai H, Miyaura C, Pilbeam CC, et al. Transcriptional induction of cyclooxygenase-2 in osteoblasts is involved in interleukin-6-induced osteoclast formation. *Endocrinology.* 1997;138:2372–2379.
 30. Richards JB, Joseph L, Schwartzman K, et al. The effect of cyclooxygenase-2 inhibitors on bone mineral density: results from the Canadian Multicentre Osteoporosis Study. *Osteoporosis Int.* 2006;17:1410–1419.
 31. Miyaura C, Onoe Y, Inada M, et al. Increased B-lymphopoiesis by interleukin-7 induces bone loss in mice with intact ovarian function: similarity to estrogen deficiency. *Proc Natl Acad Sci U S A.* 1997;94: 9360–9365.
 32. Udagawa N, Horwood NJ, Elliott J, et al. Interleukin-18 (interferon-gamma-inducing factor) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit osteoclast formation. *J Exp Med.* 1997;185: 1005–1012.
 33. Cummings SR, Black DM, Nevitt M, et al. Bone density at various sites for prediction of hip fractures. *Lancet.* 1993;341:72–75.
 34. Toogood JH, Hodsman AB, Fraher LJ, et al. Serum osteocalcin and procollagen as markers for the risk of osteoporotic fracture in corticosteroid-treated asthmatic adults. *J Allergy Clin Immunol.* 1999;104: 769–774.
 35. Rueggsegger P, Medici TC, Anliker M. Corticosteroid-induced bone loss: a longitudinal study of alternate-day therapy in patients with bronchial asthma using quantitative computed tomography. *Eur J Clin Pharmacol.* 1994;25:615–620.
 36. Toogood JH, Baskerville JC, Markov AE, et al. Bone mineral density and the risk of fracture in patients receiving long-term inhaled steroid therapy for asthma. *J Allergy Clin Immunol.* 1995;96:157–166.
 37. Israel E, Banerjee TR, Fitzmaurice GM, et al. Effects of inhaled glucocorticoids on bone density in premenopausal women. *N Engl J Med.* 2001;345:941–947.
 38. Scanlon PD, Connell JE, Wise RA, et al. Loss of bone density with inhaled triamcinolone in lung health study II. *Am J Respir Crit Care Med.* 2004;170:1302–1309.
 39. Li JTC, Ford L, Chervinsky P, et al. Fluticasone propionate powder and lack of clinically significant effects on hypothalamic-pituitary-adrenal axis and bone mineral density over 2 years in adults with mild asthma. *J Allergy Clin Immunol.* 1999;103:1062–1068.
 40. Hubbard RB, Smith CJ, Smeeth L, et al. Inhaled corticosteroids and hip fracture: a population-based case-control study. *Am J Respir Crit Care Med.* 2002;166:1563–1566.
 41. Suissa S, Baltzan M, Kremer R, Ernst P. Inhaled and nasal corticosteroid use and the risk of fracture. *Am J Respir Crit Care Med.* 2004;169: 83–88.
 42. Hanania NA, Chapman KR, Sturtridge WC, et al. Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol.* 1995;96:571–579.
 43. Fuhlbrigge AL, Bae SJ, Weiss ST, et al. Cost effectiveness of inhaled steroids in asthma: impact of effect on bone mineral density. *J Allergy Clin Immunol.* 2006;117:359–366.
 44. Sorkness CA. Establishing a therapeutic index for the inhaled corticosteroids, part II: comparisons of systemic activity and safety among different inhaled corticosteroids. *J Allergy Clin Immunol.* 1998;102: S52–S64.
 45. Kelly HK. Potential adverse effects of the inhaled corticosteroids. *J Allergy Clin Immunol.* 2003;112:469–478.
 46. Daley-Yates PT, Richards DH. Relationship between systemic corticosteroid exposure and growth velocity: development and validation of a pharmacokinetic/pharmacodynamic model. *Clin Ther.* 2004;26: 1905–1919.
 47. Adinoff A, Hollister JR. Steroid-induced fractures and bone loss in patients with asthma. *N Engl J Med.* 1983;309:265–268.
 48. Walsh WJ, Wong CA, Osborne J, et al. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. *Thorax.* 2001; 56:279–284.
 49. Sharma PK, Malhotra S, Pandhi P, Kumar N. Effect of inhaled steroids on bone mineral density: a meta-analysis. *J Clin Pharmacol.* 2003;43: 193–197.
 50. Shaker JL, Lukert BP. Osteoporosis associated with excess glucocorticoids. *Endocrinol Metab Clin N Am.* 2005;34:341–356.
 51. Buckley LM, Leib ES, Cartularo KS, et al. Calcium and vitamin D3 supplementation prevents bone loss in the spine secondary to low-dose corticosteroids in patients with rheumatoid arthritis. *Ann Intern Med.* 1996;125: 961–968.
 52. Luckert BP, Johnson BE, Robinson RG. Estrogen and progesterone replacement therapy reduces glucocorticoid-induced bone loss. *J Bone Miner Res.* 1992;7:1063–1069.
 53. Farguhar C, Marjoribanks J, Lethaby A, Suckling JA, Lamberts Q. Long term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev.* 2009;(2):CD004143.
 54. Kanis JA, Burt N, Cooper C, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporosis Int.* 2008;19:399–428.
 55. Reid RR. Preventing glucocorticoid-induced osteoporosis. *N Engl J Med.* 1997;337:420–421.
 56. Djokanovic N, Klieger-Grossman C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? *J Obstet Gynaecol Can.* 2008;30:1146–1148.
 57. Levy S, Fayed I, Taguchi N, et al. Pregnancy outcome following in utero exposure to bisphosphonates. *Bone.* 2009;44:428–430.
 58. Adachi JD, Bensen WG, Brown J, et al. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N Engl J Med.* 1997;337: 382–387.
 59. Pitt P, Li F, Todd P, et al. A double blind placebo controlled study to determine the effects of intermittent cyclical etidronate on bone mineral density in patients on long term oral corticosteroid treatment. *Thorax.* 1998;53:351–356.
 60. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. *N Engl J Med.* 1998;339:292–299.
 61. Sambrook PN, Kotowicz M, Nash P, et al. Prevention and treatment of glucocorticoid-induced osteoporosis: a comparison of calcitriol, vitamin D plus calcium, and alendronate plus calcium. *J Bone Miner Res.* 2003;18:919–924.

62. Cohen S, Levy RM, Keller M, et al. Risedronate therapy prevents corticosteroid-induced bone loss. *Arthr Rheum.* 1999;42:2309–2318.
63. Wang WQ, Ip MS, Tsang KW, Lam KS. Antiresorptive therapy in asthmatic patients receiving high-dose inhaled steroids: a prospective study for 18 months. *J Allergy Clin Immunol.* 1998;101:445–450.
64. Reid DM, Devogelaer JR, Saag K, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomized controlled trial. *Lancet.* 2009;373:1253–1263.
65. MacLean C, Newberry S, Maglione M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med.* 2008; 148:197–213.
66. Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M. Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis. *Health Tech Assess.* 2007;11:1–231.
67. Bone HG, Hosking D, Devogelar JP, et al; Alendronate Phase III Osteoporosis Treatment Study Group. 2004. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med.* 2004;350:1189–1199.
68. Jilka RL, Weinstein RS, Bellido T, et al. Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. *J Clin Invest.* 1999;104:439–446.
69. Taylor KA, Saag KG, Shane E, et al. Active comparator trial of teriparatide versus alendronate in the treatment of glucocorticoid-induced osteoporosis. *J Clin Densitom.* 2007;10:218.
70. Black DM, Greenspan SL, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med.* 2003;349:1207–1215.
71. Grey A, Reid IR. Differences between the bisphosphonates for the prevention and treatment of osteoporosis. *Thera Clin Risk Manag.* 2006;2:77–86.
72. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. www.nof.org. Accessed 2008.
73. Sambrook P, Birmingham J, Kelly P, et al. Prevention of corticosteroid osteoporosis: a comparison of calcium, calcitriol, and calcitonin. *N Engl J Med.* 1993;328:1747–1752.

Requests for reprints should be addressed to:
David Weldon, MD
Scott & White Clinic
Department of Allergy and Pulmonary Services
1600 University Dr E
College Station, TX 77840
E-mail: dweldon@swmail.sw.org

Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: ACAAI designates each Annals CME Review Article for a maximum of 2 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity. The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

CME Examination

1–5, Weldon D. 2009;103:3–11.

CME Test Questions

1. Which of the following is not indicated for the treatment of corticosteroid-induced osteoporosis?
 - a. alendronate
 - b. risedronate
 - c. zoledronic acid
 - d. ibandronate
2. All of the following should be considered for the prevention of osteoporosis due to corticosteroids except:
 - a. teriparatide (PTH 1–34)
 - b. calcium supplementation of at least 1,200 mg/d
 - c. using dual agents (inhaled corticosteroids and long-acting β -agonists) for management of at-risk asthmatics
 - d. assessing age-related risk factors (eg, gonadal hormone deficiency)
3. In children before puberty, significant effects on eventual adult height may be seen with how many oral or systemic corticosteroids “bursts” per year?
 - a. 1
 - b. 2
 - c. 3
 - d. All will eventually attain anticipated height.
4. All of the following immune modulators have an effect on bone metabolism except:
 - a. interleukin 1
 - b. interleukin 5
 - c. transforming growth factor β
 - d. tumor necrosis factor
5. Which of the following are true?
 - a. Children who received intermittent oral corticosteroids were more likely than those who received alternate-day corticosteroids to develop osteopenia.
 - b. Inhaled beclomethasone and ciclesonide administered as hydrofluoroalkane agents are equal in their probability to induce growth suppression in children.
 - c. A z score of -1 to -2.5 defines osteopenia on dual x-ray absorptiometry.
 - d. The risk of future fractures in corticosteroid-treated patients is less with bisphosphonates than hormone replacement therapy.

Answers on page 50.