

Louisiana Drug Utilization Review (LADUR) Education

Glucocorticosteroids and Osteoporosis

Bill Ross, BS Pharm.
Clinical Coordinator for Drug Information Louisiana Drug and Poison Information
Center
School of Pharmacy University of Louisiana at Monroe

Issues:

- Osteoporosis is a progressive systemic skeletal disorder.
- Primary osteoporosis is found in both sexes at all ages, but frequently follows menopause in women and occurs later in life in men.
- Adequate intake of calcium and vitamin D is essential to the development of optimal peak bone mass and to the preservation of bone mass throughout life.

OVERVIEW

The first documented observation of skeletal decalcification resulting from adrenal hyperplasia secondary to ACTH-producing pituitary tumors was reported by Cushing in 1932. (27) Osteoporosis may be defined as a progressive systemic skeletal disorder characterized by low bone mass, microarchitectural deterioration of bone tissue, with resulting compromised bone strength predisposing a person to an increased risk of fracture. (1,19) Two primary factors, bone density and bone quality, constitute bone strength. Bone density is defined as grams of mineral per area or volume and is individually determined by peak bone mass and amount of bone loss. Factors such as architecture, turnover, damage accumulation (e.g., microfractures), and mineralization constitute bone quality. (1) There is no current accurate measure of overall bone strength. A frequently used proxy measure is bone mineral density (BMD) and accounts for approximately 70% of bone strength. The World Health Organization (WHO) defines osteoporosis as bone density 2.5 standard deviations below the mean for young white adult women. How this diagnostic criterion is to be applied to men and children and across ethnic groups is unclear. (1) Primary osteoporosis is found in both sexes at all ages, but frequently follows menopause in women and occurs later in life in men. Secondary osteoporosis, in contrast, results from the effects of medications such as glucocorticoids, conditions such as hypogonadism, or diseases such as celiac disease. An osteoporotic fracture is result of a failure-inducing force such as trauma applied to compromised osteoporotic bone. Such traumatic events range from normal lifting and bending to high-impact falls and can have profound physical, financial, and psychosocial consequences. Approximately one third of patients with hip fractures are discharged to nursing homes within one year following a fracture and only one third of patients regain their prefracture level of function. Within a year after an osteoporotic hip fracture, 20% of affected patients are no longer

living. The treatment of osteoporotic fracture in the United States involves an estimated direct expenditure of \$10 to \$15 billion annually. These figures may severely underestimate the actual costs because they do not include the indirect costs of lost wages or productivity of either the patient or the caregiver. (1) The prevention of osteoporosis is multi-factorial and begins early in life. Adequate intake of calcium and vitamin D is essential to the development of optimal peak bone mass and to the preservation of bone mass throughout life. Additionally gonadal steroids are important determinants of peak and lifetime bone mass. Regular exercise, especially high-impact and resistance activities, are critical to development of high peak bone mass and may reduce risk of falls in the elderly. (1) This paper will review the relationship between corticosteroids (glucocorticoids) and osteoporosis. The adrenal cortex produces both glucocorticoids, primarily hydrocortisone, and mineralocorticoids, primarily aldosterone. (31) Publications relative to adrenal hormones and osteoporosis frequently use the general term "corticosteroids", but there is no credible clinical evidence of a contribution of mineralocorticoids to development of osteoporosis. Consequently this review relates to glucocorticoids, although the term corticosteroid will also be used to designate glucocorticoids.

Pathophysiology

Bone tissue is subject to a constant metabolic turnover and remodeling process throughout adulthood, and this process reflects a fine balance in the bone matrix in terms of the activity of bone-forming (osteoblasts) and bone-breakdown cells (osteoclasts). (22) Glucocorticoids decrease bone formation and increase bone resorption via variable processes. Corticosteroids directly inhibit osteoblast function at the glucocorticoid receptor. This alteration of function causes a decrease in replication, differentiation, proliferation, and life span of osteoblasts. As a result the total amount of bone restored during each remodeling cycle is decreased by 30%, resulting in diminished mean wall thickness. Additionally, glucocorticoids enhance the activity and increase the number of osteoclasts, which results in a greater number of active resorption surfaces. (9) Dose-dependant calcium malabsorption has also been demonstrated in steroid-treated patients as a result of direct impairment of the intestinal cell calcium transport process. (10) Decreased calcium absorption is evident within the first two weeks of glucocorticoid therapy. (11) A secondary hyperparathyroidism may then occur with urinary calcium excretion double that of non-steroid treated patients. (10) In addition, corticosteroids reduce levels of prostaglandin E₂, insulin-like growth factors, phosphate, type 1 collagen, and non-collagens including osteocalcin. (12, 13)

Estrogen in women and both androgen and estrogen in men determine both peak and lifetime bone mass. (1, 3) Bone loss from the total hip was eight times as great in elderly women with estradiol levels below 5 pg per milliliter as in women with levels of 10 pg per milliliter or greater. Glucocorticoid alteration of gonadal hormone levels is multifactorial with effects on the pituitary, gonads, and adrenal glands. Pharmacologic doses affect the pituitary by inhibiting the

response of leuteinizing hormone, the gonadotropin-releasing hormone, thereby decreasing gonadal hormone production. Glucocorticoids may also directly inhibit gonadal hormone production. Adrenal hormone production is inhibited through suppression of corticotrophin secretion and the production of androstenedione, a substrate for both testosterone and estrone. (3) Men treated with glucocorticoids were shown to have testosterone concentrations of only 50% of those of a control group. (9)

Risk Factors

Bone loss becomes evident if the bone resorbed is not fully replaced due to over activity of the osteoclast or under activity of the osteoblast. Functional capability of osteoblasts and osteoclasts may be assessed by bone cell markers such as serum bone specific alkaline phosphatase, osteocalcin, type I procollagen peptides (bone formation), and serum or urine pyridinoline crosslinks (bone resorption). (20)

Biochemical determinants of bone formation include levels of alkaline phosphatase, osteocalcin, procollagen type 1 carboxyterminal and aminoterminal propeptide, and procollagen type 3 aminoterminal propeptide; all of which are serum determinations. Markers of bone resorption include levels of urinary hydroxyproline, urinary or serum pyridinium, cross-links, urinary collagen type 1 cross linked N-telopeptide, urinary collagen type 1 cross-linked C-telopeptide (crosslaps), and serum carboxyterminal telopeptide of type 1 collagen. Generally bone formation markers are more sensitive than bone resorption markers for determining the effect of glucocorticoids, with osteocalcin being the marker of choice because of its sensitivity, specificity, and reproducibility. However bone markers cannot be used without reserve as a surrogate for bone density to predict the risk of development of osteoporosis. (22) A small study of adult asthmatic patients, treated with oral and inhaled glucocorticoids, evaluated osteocalcin and procollagen as markers for the risk of osteoporotic fracture. Results indicated that neither of these two markers proved sufficiently accurate to be reliable as indicators for fracture risk in elderly, corticosteroid-treated asthmatic adults. (18)

General risk factors associated with low BMD include age, ethnic origin, gender, diet (primarily inadequate calcium and vitamin D intake), physical activity, thyroid status (history of hyperthyroidism), sex hormone status, low weight and body mass index (being in the lowest quartile in weight, ≤ 57.8 kg, thinness), family history of osteoporosis, history of smoking, prior fracture history after the age of 40, history of a fracture at the hip, wrist, or vertebra in a first degree relative, and possibly ethanol and caffeine consumption. (1, 19, 22) Both men and women experience an age-related decline in BMD beginning around midlife. In the early years following menopause, women experience more rapid bone loss, which places them at earlier risk of fractures. This group experiences almost three quarters of all hip fractures and has the highest age-adjusted incidence of fracture. In men, hypogonadism is also an important risk factor. Men and

perimenopausal women with osteoporosis more commonly have secondary causes for bone loss than do postmenopausal women. The incidence of osteoporosis is highest in Caucasian and Oriental women and lowest in women of African descent. Mexican-American women have BMDs between those of white non-Hispanic women and African American women. Based on limited available data, Native American women have lower BMDs than white non-Hispanic women. (1)

Contribution of Glucocorticoids to Osteoporosis

Osteoporosis is reported to occur in more than 50% of patients who receive long-term glucocorticoid therapy. Risk of bone fracture is two to four times higher in patients taking glucocorticoids than that in glucocorticoid-naïve patients. The overall estimates of fracture secondary to steroid therapy range from 30 to 50%. (9) Results of cross-sectional studies suggest that minimally one in four long-term corticosteroid users sustain osteoporotic fractures. The prevalence of vertebral fractures is 11% among asthma patients who receive steroid therapy for at least one year. Patients ingesting 7.5 mg per day or more of prednisone for six months or longer risk rapid bone loss from the hip, spine, and forearm. (28) Some evidence exists, however, that these adverse effects of glucocorticoids on bone may be reversible. A study by Laan et al (29) demonstrated that in patients receiving \leq 10 prednisone per day for 18 months, there was a significant but incomplete reversal of bone loss once the prednisone was discontinued.

Glucocorticoids exert the greatest effect at skeletal sites with a higher proportion of trabecular bone than cortical bone, probably because trabecular bone has an inherently higher turnover rate than cortical bone. (3) This is not always the case, however, as demonstrated in the study by Israel et al in which glucocorticoids affected the total hip and the trochanter but not the spine. (4)

Oral glucocorticoid alteration of bone mineral density is dose-related and seen early in the course of treatment. (3) Bone reduction is dose-dependent and time-dependent and occurs most rapidly during the first six to 12 months of therapy. On average 5% of bone mass is lost within the first year of therapy; thereafter, the annualized rates of loss range from 0.3% to 3%. It has been demonstrated that daily doses of oral prednisone greater than or equal to 7.5 mg, or cumulative doses greater than 10 grams, cause the most significant detrimental effect, with no risk reduction with alternative-day administration. (9) An oral dose of prednisolone as low as 2.5 mg per day has been associated with an increased risk of vertebral fracture. (3) The relationship of inhaled glucocorticoids with osteoporosis is less clear, but a study by Israel et al documented adverse effects on bone density in women without other apparent risk factors for bone loss (4) These findings are supported by the recent investigation between the use of inhaled corticosteroids and an increased risk of nonvertebral, hip, and vertebral fractures. (3)

A four-year longitudinal study by Masumato et al evaluated the effect of inhaled

beclomethasone dipropionate and short-term oral corticosteroid therapy on lumbar bone density. Generally lumbar bone density remained unchanged regardless of dose, whereas the Z score (i.e., the percentage of normal value predicted from age and sex) increased significantly. Patients receiving frequent oral doses demonstrated significantly greater loss in BMD and Z score compared with those receiving sporadic courses. (2) A decrease in bone density associated with the daily dose of inhaled corticosteroid and extended years of prednisone use was demonstrated in a cross-sectional study of asthmatic adults. Interestingly, a subgroup analysis of 41 postmenopausal asthmatic women from this study found that increased bone density was associated with the number of years of supplemental estrogen therapy received, suggesting that estrogens may have a protective effect against glucocorticoid-induced osteoporosis. (23) A comparison of effects of fluticasone and budesonide in dry powder inhalers in healthy versus asthmatic subjects (5) found that budesonide significantly reduced osteocalcin in both groups relative to fluticasone. These results suggest that fluticasone and budesonide may have differential effects on bone metabolism. In a placebo-controlled study of inhaled triamcinolone in COPD, patients taking triamcinolone had a higher percentage decrease from base line in femoral and lumbar bone density compared to the placebo group. (6) In a small randomized but open parallel study, inhaled fluticasone propionate (500 micrograms twice daily) and budesonide (800 micrograms twice daily) were evaluated in adults with moderate to severe asthma relative to effects on biochemical markers for bone turnover, as well as changes in bone mineral density. Results demonstrated no evidence of a significant difference between the inhaled steroids on bone markers of bone resorption and formation or bone mineral density during the 12-month study with either fluticasone or budesonide. (25) In a small placebo controlled trial, Li et al evaluated the effect of inhaled fluticasone propionate powder on the hypothalamic-pituitary-adrenal axis and bone mineral density over a two year period in adult asthma patients. (21) Study results suggested that this glucocorticosteroid, dosed at 500 micrograms twice daily for up to two years, was efficacious and well tolerated and produced no clinically relevant effects on the hypothalamic- pituitary-adrenal axis or bone density. In a pharmacoeconomic review, inhaled fluticasone in recommended doses does not appear to reduce bone mineral density in adults or to reduce growth in children between the ages of four and 14 years. (7) An additional finding was that fluticasone produced equivalent or reduced effect on this end point compared to both beclomethasone and budesonide and had similar effects to sodium cromoglycate on bone growth in children. A small multicenter trial involving moderate asthmatic patients evaluated the effect of fluticasone (400 and 750 mcg. per day) and beclomethasone (800 and 1500 mcg per day) on bone density and bone metabolism. The prospective data for this year-long study show that inhaled corticosteroids, within study parameters, had no adverse effects on bone mass and metabolism (16). An investigation of 157 asthmatic children who received inhaled budesonide for three to six years, determined that bone density measurements did not differ significantly compared with those of asthmatic control subjects who had not received steroids. (24) Wong et al (8), in a cross-

sectional study, evaluated inhaled corticosteroid use and bone-mineral density in asthma patients. Beclomethasone was used by 80% of the study subjects. Confounding variables were minimized by using young patient subjects with mild asthma and by excluding those who had received more than two courses of oral corticosteroids. A doubling of cumulative dose resulted in a decrease in both lumbar and femoral bone mineral density compared with age-matched reference data.

A number of glucocorticoids are administered intranasally rather than by multidose inhaler devices. In a review of the systemic effects of intranasal steroids (9), Allen notes that harmful effects of intranasal steroids on bone metabolism have not been adequately evaluated but are unlikely.

Treatment

Oral bisphosphonates are generally considered a first-line therapy for glucocorticoid-induced osteoporosis (31). The three bisphosphonates currently marketed in the United States include alendronate (Fosamax), etidronate (Didronel), and pamidronate (Aredia), which is available only in a parenteral form. Currently risedronate (Actonel) is FDA approved for both prevention and treatment and alendronate has approval for treatment of glucocorticoid-induced osteoporosis. Various studies suggest that these drugs reduce bone loss in men and women and lower the rate of fracture in patients with osteoporosis. (3) Interpreting study results can be difficult at times because of varying bisphosphonates and regimens, the heterogeneity in study populations, the effect of underlying disease on bone, and concomitant therapeutic interventions. (9) Information on the impact of bisphosphonates on the risk of glucocorticoid-induced fractures is limited and not conclusive, since most of the trials have been of 2 years or less in duration and insufficiently powered to show fracture reduction. It appears that postmenopausal women not taking estrogen supplementation seem to benefit most from taking bisphosphonates for the prevention of bone loss and vertebral fractures in corticosteroid-induced osteoporosis. (9) A recent meta-analysis indicates that in patients at risk for glucocorticoid induced fractures, bisphosphonates have shown some of the best evidence for reducing bone loss, particularly at the lumbar spine. It was concluded that bone density changes correlate with fracture risk in patients with corticosteroid-induced osteoporosis, but there are insufficient data to make conclusions regarding fracture risk reduction and the use of bisphosphonates. (14) In an earlier small placebo controlled study etidronate and calcium supplements were evaluated for impact on bone density in adult asthma patients receiving long-term high-dose inhaled glucocorticoids. Endpoints were bone density and changes in bone cell markers. Study results suggested that inhaled corticosteroids under study parameters induce bone loss that is preventable with calcium supplementation with or without etidronate. (26) A recent multi-arm clinical trial evaluated the cost effectiveness of calcium and vitamin D supplementation, etidronate, and alendronate in the prevention of vertebral fractures in women receiving glucocorticoids. Data analysis indicated that calcium and vitamin D supplements and low cost bisphosphonate therapy such as

cyclic etidronate decrease the life-time vertebral fracture risk at acceptable costs and should be considered when beginning glucocorticoid therapy in women. (34)

In a placebo controlled trial alendronate, with concomitant administration of calcium and vitamin D, was evaluated for the prevention and treatment of glucocorticoid-induced osteoporosis. Using endpoints of BMD and bone fractures, the authors concluded that although alendronate does prevent progressive osteopenia in this population, it has not been proved to prevent vertebral compression or hip fractures (17) In a randomized, multicenter, open-label trial with 195 subjects, alendronate, calcitriol, and simple vitamin D were compared in the prevention and treatment of glucocorticoid-induced bone loss. The resulting data do not suggest any difference between vitamin D and calcitriol but demonstrate that alendronate was superior to either treatment for glucocorticoid-induced bone loss. (33)

Raloxifene (Evista) is the only selective estrogen-receptor modulator that has been approved for the prevention and treatment of osteoporosis. This agent has been shown to be effective in the prevention of vertebral (but not non-vertebral) fractures in postmenopausal women. (31) Use in patients with osteoporosis secondary to corticosteroids has not been evaluated.

Calcitonin is a naturally occurring peptide that at pharmacologic doses inhibits osteoclastic activity and thus acts as an anti-resorptive drug. In preventive studies calcitonin reduced bone loss secondary to glucocorticoid therapy, but did not lead to a net gain in bone mineral density. Among osteoporotic patients or those on long-term glucocorticoids, calcitonin produced a net gain in BMD, although no data addresses the incidence of fractures. (30) Currently calcitonins are not FDA approved for this purpose.

Parathyroid hormone was first investigated for the treatment of clinical osteoporosis over 20 years ago, but studies since then have been limited. One investigation of parathyroid hormone (teriparatide or Forteo) for the treatment of glucocorticoid-induced osteoporosis demonstrated a significant increase in BMD in the lumbar spine and an insufficient gain in the femoral neck. (31) A recent review of randomized clinical trials concluded that parathyroid hormone reduces vertebral fractures and increases spinal bone density in glucocorticoid-induced osteoporosis, but at the expense of decreased radius-bone density. (32)

Dietary or supplemental calcium and vitamin D intake is essential for the prevention of osteoporosis, but should not be used as sole therapy. (31) The American College of Rheumatology Task Force Guidelines (15) recommends calcium supplementation of 1500 mg per day in these patients, and patients at risk for vitamin D deficiency may also require supplementation.

Specific Recommendations for Prevention and Management

Assessment of bone mass, identification of fracture risk, and additional risk parameters for patients to be treated are determinants when evaluating patients

for glucocorticoid-induced osteoporosis. (1) Pharmacologic prophylaxis should be considered in all patients beginning high-dose (>7.5 mg/day) prednisone (check equivalent doses) long-term (> six months) glucocorticoid therapy. Guideline recommendations suggest a baseline BMD measurement of all patients with dual energy x-ray absorptiometry (DXA) to ascertain the risk of osteoporosis and to monitor the efficacy of preventive measures throughout the course of therapy. BMD measurements may be repeated in six to 12 months depending on initial bone mass. Initial pharmacotherapy should be reevaluated if BMD has decreased by more than 5% from baseline. Prior to considering a dose form change to oral dosing, dose maximization of inhaled and topical corticosteroids is recommended. Preventive lifestyle modifications include smoking cessation, maintenance of healthy body weight, regular weight-bearing exercise, decreased alcohol consumption, sodium restriction, and increased calcium intake. (9)

American College of Rheumatology Task Force Guidelines (15)

Topical or inhaled glucocorticoids should be used instead of oral preparations when possible. Protection does not appear to be afforded by use of alternate-day therapy. Baseline bone mineral densitometry should be performed before long-term steroid therapy or very soon thereafter. Ideally an anteroposterior dual-energy x-ray absorptiometry measurement of both the lumbar spine and femoral neck should be done. If only one site measurement can be obtained, it is recommended that the lumbar spine be measured in men and women less than 60 years old and the femoral neck in men and women older than 60 years because in the older patients the lumbar measurements are not as reliable as those of the femoral neck. Postmenopausal women taking glucocorticoids should take hormone replacement therapy, if no contraindications exist. Premenopausal women who experience oligomenorrhea or amenorrhea while taking corticosteroids should consider oral contraceptives absent contraindications. Testosterone levels should be measured in men who are receiving glucocorticoids. Patients treated with corticosteroids should also take 1500 mg per day of a calcium supplement along with vitamin D supplementation for at risk patients. (15)

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