
Clinical and diagnostic features of glucocorticoid-induced osteoporosis

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ABSTRACT

Glucocorticoid (GC) treatment is associated with a 50-60% increase in the risk of hip fracture and a 2-3 fold increase in the risk of vertebral fractures in adults. Bone loss occurs early in GC treatment, and although some recovery of bone mass occurs with time, complete recovery is unlikely. Patients who already have low bone mass are the group that are most susceptible to fracture. Fracture rates are highest in postmenopausal women, especially those who are not receiving hormone replacement therapy, but are also increased in men and premenopausal women. Therapies are now available to prevent GC-induced bone loss and should be employed early in GC treatment.

Glucocorticoid treatment and changes in bone density

Glucocorticoid (GC) treatment is associated with many unwanted effects but osteoporosis and fractures are the most serious adverse events (1). Trabecular bone (primarily in the spine and ribs) is more metabolically active than cortical bone (found in the hip and long bones) and therefore more susceptible to the negative effects of such factors as estrogen withdrawal and GC use. Trabecular bone loss occurs early in GC treated patients, with the highest rates of bone loss seen in the first 3-6 months of treatment (10-20%) followed by a slower rate of

loss (2% per year) over time (2-4). Bone loss at the femoral neck occurs more slowly (2-3% in the first year) but continues over time. Bone loss at both sites is also dose-related, with higher doses of GC causing greater bone loss. Inhaled GC appear to have minimal effects on BMD (Figs. 1-2).

Fracture rates

Fracture rates have been reported to be increased by 50-100% at the hip and 4 to 5-fold at the spine in GC treated patients (5-12). The incidence of vertebral fractures varies in studies depending on the criteria used to define a vertebral fracture. Some studies use radiographic changes of vertebral size (only 25% - 33% of which have clinical symptoms) and this is the endpoint most commonly used in clinical trials. Other studies use clinically reported vertebral fractures as an endpoint. Naganathan and colleagues studied thoracolumbar x-rays in 229 patients who received GC treatment for more than 6 months and reported that 28% of patients had a least one vertebral fracture and the incidence increased with age (13). These data are similar to those from the Arthritis and Aging Medical Information System (ARAMIS), which found that 33% of women with rheumatoid arthritis had a clinical fracture after 5 years of follow-up (14).

Van Staa and colleagues conducted a large retrospective study in the U.K.

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- Σ Greater bone loss in trabecular bone than cortical bone
 - Σ Greatest bone loss occurs in the first 3 to 6 months
 - Σ Vertebral fracture risk increased 3- to 5-fold
 - Σ Femoral fracture risk increased 50-60%
 - Σ Fractures most common in postmenopausal women, but men and premenopausal women are also at risk

Fig. 1. Clinical features of glucocorticoid-induced osteoporosis.

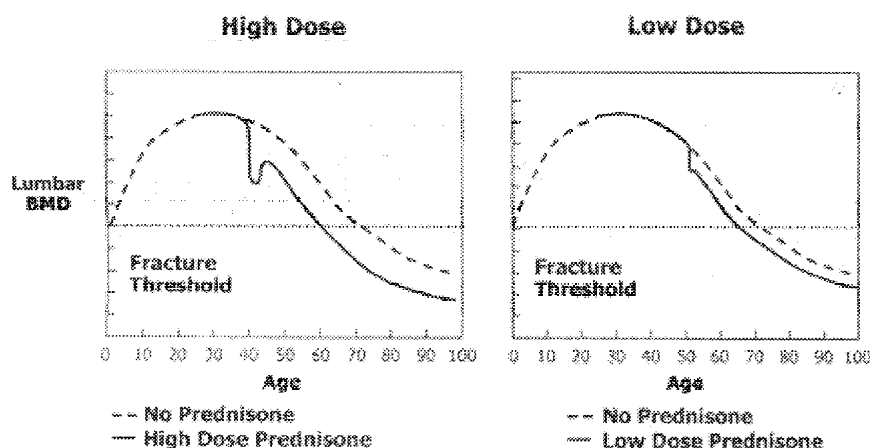


Fig. 2. Schema of bone loss due to high and low dose glucocorticoids.

comparing clinically detected fracture rates in 244,235 GC users and in 244,235 matched controls (15). Among the current GC users, the relative risk (RR) of hip and vertebral fractures was 1.6 and 2.6, respectively. In addition, they found a dose dependent effect of GC treatment on fracture rates, with no increase in the hip fracture risk with doses of prednisone of less than 2.5 mg per day, a RR of 1.77 with doses of 2.5-7.5 mg per day, and a RR of 2.27 with doses greater than 7.5 mg. In contrast, the vertebral fracture risk was increased to 1.55 in patients taking prednisone at a dose of less than 2.5 mg/d, the RR was 2.59 with a prednisone dose of 2.5-7.5, and the RR was 5.18 with doses greater than 7.5 mg. There has been a great deal of interest in whether there is a "safe" dose of oral GCs that does not cause bone loss. This data suggests that even the lowest doses of prednisone are associated with vertebral bone loss, but because this was a retrospective case review it is unclear whether the fractures reported in patients on very low doses was due to bone loss from previous use of higher doses.

Although the greatest bone loss occurs in young patients, fracture rates in GC treated patients are highest among patients who begin GC treatment and who already have low bone mass, such as postmenopausal women. Van Staa and colleagues also reported that the risk of fracture for women was greatest after age 50 and increased exponentially with age to an incidence of 4.5 fractures per 100 patient years at age 85 (15).

Fracture rates in GC treated patients are

higher than would be expected from the observed changes in bone density (10, 11). In one study, the vertebral fracture rate was increased 6-fold with a decrease of less than 1 SD in spine BMD (12). This suggests that GC treatment may lead to fractures through skeletal effects that cannot be measured by bone density testing (such as changes in bone architecture) or through non-skeletal effects such as loss of muscle mass, balance problems, or immobility. Van Staa reported that there was a higher risk of falling among GC users (RR = 2.8) suggesting one possible extra-skeletal cause of higher fracture rates (15).

Recovery of bone mass after glucocorticoid treatment

Bone mass can increase or "recover" after corticosteroid treatment is withdrawn. In 1987, Pocock and colleagues reported spontaneous increases in bone density in patients after treatment of endogenous Cushing's disease (16). In a cross sectional study of patients with rheumatoid arthritis, the spine BMD among former users of GCs was higher than that of current users. In a prospective study of bone density in patients with rheumatoid arthritis receiving treatment with low dose corticosteroids, lumbar spine BMD increased significantly after withdrawal of GC treatment but hip BMD returned to the level of normal controls (17).

Van Staa reported a declining nonvertebral fracture relative risk of 2.4 and 1.8 in the first and second years after termination of high dose GC treatment (15). However, long term projections of non-

vertebral fracture risks 5 years after GC use reveal rates that are 20% greater than in controls. These data suggest that recovery of bone mass occurs, but is limited and that the lifetime fracture risk is increased years after GC treatment is stopped.

Glucocorticoid use and children

The natural history of the effects of GC treatment has not been as well described in children as in adults. GC treatment effects on body weight, growth velocity, bone density, and muscle mass, and sexual maturation in children are all factors which contribute to the acquisition of peak bone mass and future fracture risk. Bradley and Ansell reported that the fracture rate in GC treated children with systemic juvenile chronic arthritis (JRA) was 20% compared to 1% in non-GC treated children (18,19). They also found that growth delay and low bone density were associated; the mean height of children with crush fractures was at the 6th percentile as compared to the 30th percentile for children with no crush fractures. Varonos and Ansell demonstrated that there was a linear relationship between the GC dose and the time to first fracture in children with JRA ($r = -0.67$, $p < 0.001$) (20).

Crush fractures were also more common in children receiving more than 5 mg of prednisone per day or a dose of 0.1 mg/kg (21). In another study, the lumbar spine BMD of 40 children with JRA was lower than that of age-matched control children (0.685 g/cm² versus 0.722 g/cm²), and the BMD of GC treated children was lower than that of children receiving NSAIDs (0.623 g/cm² and 0.710 g/cm² respectively) (22).

The extent of recovery of growth velocity and bone mass in children after the termination of CS is unknown. Some information is available from a case report of identical twin girls, one of whom had endogenous Cushing's syndrome which was untreated from the age of 10 to 15 years (23). The lumbar spine BMD of the affected twin was -3.2 SD below the mean for age and increased by 39.5% and 24.2% in the lumbar spine and femoral neck, respectively, after treatment. After 27 months of follow up there were large differences between the twins in all

the measures of bone mass examined, suggesting that the recovery of height velocity and bone density was not complete.

GC treatment can decrease the childhood growth rate, which is an important predictor of adult fracture rates. In a large retrospective study from Helsinki, subjects with a childhood growth rate more than 1 SD below the mean for the cohort had a greater than 4-fold increase in the risk of fracture (RR = 4.6, CI 1.4 - 14.7) (24). Chesney and colleagues reported that GC treated children with renal disease had a growth velocity that was only 60% of that of non-GC treated children (25). Children who stopped GC treatment had an increase in bone mineral content and height - "catch up" growth - but the study was not long enough to determine whether the children experienced full recovery of the predicted height. In another small study, the mean height z score of GC treated children was -0.5, and their bone age was 1.5 years behind their chronologic age (26). In a study of children with JRA, Hopp found that patients receiving GC had both lower BMD and shorter stature (27). The effects of the dose, duration, and timing of GC treatment (especially with respect to pubertal development) on the acquisition of adult bone mass are still unclear in children.

Diagnostic evaluation

Numerous professional and patient organizations advocate baseline bone density testing when a patient will receive GC treatment for more than 6 months at a dose of more than 7.5 mg prednisone per day. In addition, basic metabolic testing should be done, including serum calcium, phosphorus, alkaline phosphatase, creatinine, liver function tests, thyroid function tests and the 25 OH vitamin D level (or 1,25 vitamin D level in patients with renal insufficiency). Hypogonadism is not uncommon in GC treated patients. GC treatment has also been associated with lower levels of sex hormones in both men and women (28-30). Other factors that increase bone loss should be looked for, including immobility, anti-convulsant use, and other medical con-

ditions that can affect vitamin D metabolism, such as the renal disease and malabsorption which can be seen in patients with inflammatory bowel disease.

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