Prevention and treatment of glucocorticoid-induced osteoporosis

Compiled by the Board of Osteoporosis New Zealand with input from colleagues throughout New Zealand

Introduction

Glucocorticoids result in fractures in about a third of chronic users. Short-term use (days to weeks) seldom results in clinically significant skeletal changes.

Pathogenesis

These agents interact with bone and calcium metabolism at many levels,[1] in particular they reduce the osteoblast's synthesis of collagen and the other proteins of bone matrix and reduce osteoblast survival. Glucocorticoids also cause malabsorption of calcium in the gut and the renal tubule, and reduce sex hormone concentrations, particularly in men and postmenopausal women.

Effects on the skeleton

Glucocorticoids cause marked bone loss in the first few months of steroid treatment, especially in trabecular bone (up to 30% in some studies). Cross-sectional studies of long-term users demonstrate bone densities 10-20% below normal, the distribution remaining unimodal which suggests that most individuals lose bone to a similar extent. Thus, an individual's bone density while taking steroids is determined by their pre-treatment density, which in turn will reflect their age, sex, race, body weight and underlying disease. Density is also influenced by the cumulative glucocorticoid dose. Fractures occur predominantly at sites rich in trabecular bone, such as the vertebral bodies and ribs, though hip fracture risk is also increased three-fold by these drugs. Patients also receiving other immunosuppressive agents (e.g. after organ transplantation, autoimmune disease) are particularly at risk, since these agents also contribute to the loss of bone. Although inhaled corticosteroids depress biochemical markers of bone turnover, appropriately controlled trials have not shown detrimental effects on bone density or fractures.[2]

Identification of those at risk

Most individuals using glucocorticoid drugs in doses greater than prednisone 5mg/day (or equivalent) will experience bone loss and may be at risk of fractures. The clinical risk factors cited above are of some value in identifying such patients but are only poorly correlated with bone density, which therefore should be measured directly.

Since vertebral bodies are a common site of bone loss and fracture, they are the logical place at which to measure bone density. Either dual-energy x-ray absorptiometry (DXA) or quantitative computed tomography are suitable. In patients in whom there is marked osteophytosis or scoliosis of the spine, proximal femoral densitometry should be carried out. Ultrasound assessment of the heel shows promise as a method of assessing bone loss in steroid-treated patients, but more data are necessary before this technique can be used in routine clinical practice. Measurement of biochemical markers of bone turnover has not been shown to add significantly to the assessment of steroid-induced bone loss.

Indications for treatment

If bone density T-score is <-1.5 at the spine or hip (i.e. >1.5 standard deviations below the mean value in the young normal population) pharmacologic therapy should be started. Note that the T-score threshold for intervention is higher than for postmenopausal osteoporosis because rates of bone loss are greater in steroid-treated subjects, particularly in those just starting therapy and in those taking higher steroid doses (e.g. prednisone >10 mg/day).

A past history of fracture after minimal trauma is also a major reason for weighting the balance in favour of intervention, since it implies that the individual's skeleton is already of marginal adequacy to withstand the trauma of daily living. If bone densitometry is not available, then pharmacological intervention should be offered to men and women over the age of 50 years, adults with

body weights less than 55kg, and those with a past history of fracture, who are expected to be using prednisone in a dose >5mg/day long-term. The need for ongoing prophylaxis after steroids have been discontinued should be judged by the same standards as for other individuals not taking steroids, that is, on the basis of bone density, age, fracture history and other clinical risk factors.

Interventions

Optimisation of dietary and lifestyle variables is applicable to all subjects receiving steroids. Specifically, provide calcium supplementation in those with intakes <1000mg/day, vitamin D supplementation (e.g. calciferol 1.25mg/month or 500–1000 units/day) in those with serum 25-hydroxyvitamin D<50nmol/L (<20 mg/L), and encourage smoking cessation and weightbearing exercise. Minimisation of steroid dose is always important.

Bisphosphonates (e.g. etidronate 400mg/day for two weeks every three months,[3] or alendronate 5–10 mg/day or 70 mg/week[4]) are the best documented interventions. They must be taken on an empty stomach with water alone.

Sex hormone replacement (i.e. conventional HRT in postmenopausal women,[5] or testosterone injections in the high percentage of men on steroids who are hypogonadal[6]) are also effective and can be used as sole therapies or in addition to bisphosphonates. Their balance of risks and benefits needs to be considered in making the decision to use these agents. Calcitriol has been shown to prevent spinal bone loss in some studies but not in all.[7,8] It does not appear to be as effective as the bisphosphonates in preventing bone loss at other sites, so should be used as a second-line or adjunctive therapy. In those whose bone density T-scores are in the range -1.5 to -3, intervention with a single agent is appropriate, usually a bisphosphonate or sex hormone replacement (in those with demonstrable deficiency). Since the therapeutic efficacy of these agents is comparable, the choice is based on a consideration of the patient's other medical problems, possible side-effects, and cost. Screening for breast or prostate cancer are important prerequisites to the use of sex hormone replacement. In a patient with marked bone loss, these agents can be combined with each other, and/or with other interventions such as calcitriol to produce substantial increases in bone density.

Follow-up

If the initial decision is not to treat, then a follow-up bone density measurement should be made, usually at one year. In individuals with high baseline T-scores (e.g. >+1) or low prednisone doses (e.g. <5 mg/day), two years may be more appropriate. In those starting on anti-osteoporotic therapy, follow-up bone density is usually at two to three years, but could be earlier in those on high steroid doses or in whom there are doubts regarding compliance.

Conclusion

The availability of effective interventions in this condition places a responsibility of any prescriber of glucocorticoids to assess fracture risk in their patients and to provide prophylaxis against bone loss. The widespread adoption of this strategy will result in many fewer glucocorticoid treated patients having to accept the morbidity of multiple fractures on top of that of their other medical conditions.

References

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