What to do about bones in those on prednisone?

Steroids such as prednisone, methylprednisolone, hydrocortisone and dexamethasone have many benefits and are in widespread use, particularly in the elderly population. They are affordable and potent anti-inflammatory drugs used to treat a broad spectrum of conditions.

Although the efficacy of glucocorticoids for treating a broad spectrum of inflammatory and autoimmune diseases is relatively well established, their tendency to induce potentially serious and often irreversible side effects, especially with long-term, high-dose treatment, continues to be a management challenge. While physicians attempt to place limits on the dose and duration of glucocorticoid therapy, this may not always be possible. Many patients therefore face the risk of bone loss and fractures due to glucocorticoid-induced osteoporosis.

Glucocorticoid-induced osteoporosis is the most common form of secondary osteoporosis. However, despite the fact that glucocorticoids can cause bone loss and fractures, many patients receiving or initiating long-term glucocorticoid therapy are not evaluated for their skeletal health. In addition, patients often do not receive specific preventive or therapeutic agents even after appropriate evaluation deems this appropriate.

Many factors contribute to bone loss during glucocorticoid therapy, such as underlying disease, malnutrition, vitamin D insufficiency, hypogonadism, and low body weight. Disorders for which glucocorticoids are prescribed are themselves causes of osteoporosis. Inflammatory bowel disease, rheumatoid arthritis and chronic obstructive pulmonary disease (COPD), for example, are all associated with bone loss, independent of glucocorticoid treatment. One has to take into account the underlying disease itself, along with the use of glucocorticoids, when considering the management of glucocorticoid-induced osteoporosis.

TABLE 1. EXAMPLES OF CONDITIONS TREATED WITH PREDNISONE

Dermatological
Gastrointestinal - Inflammatory bowel disease
Pulmonary - asthma, chronic obstructive pulmonary disease, interstitial lung disease
Renal - glomerulonephritis
Rheumatological - rheumatoid arthritis, lupus, vasculitis, polymyalgia rheumatica
Malignancy
Post organ transplantation

CHANGE IN BONE DENSITY AND INCREASED FRACTURE RISK

Bone loss occurs rapidly during the first few months of glucocorticoid treatment and occurs in areas of high bone turnover. Hence, trabecular bone is affected more than cortical bone. This loss continues at a slower rate with ongoing use. The mechanism of bone loss includes reduced bone formation and increased bone resorption, as well as altered production of gonadal sex hormones, inhibition of intestinal calcium absorption and enhanced renal excretion of calcium.

The risk of fracture increases rapidly in patients with glucocorticoid therapy. Fractures tend to occur at higher bone density levels than seen with postmenopausal women, suggesting that glucocorticoids have both a qualitative and quantitative effect on bone, adversely effecting bone architecture, which is not measurable using standard DEXA bone densitometry.

Glucocorticoids also cause proximal myopathy, which increases the propensity to fall, further increasing the risk of fractures. Glucocorticoid-induced myopathy may occur following early exposure to glucocorticoids. In the long term it manifests as weakness of the pelvic girdle musculature and may affect up to 60% of patients treated with glucocorticoids.

Although fractures can occur early in the course of glucocorticoid therapy, their incidence is also related to the dose and duration of glucocorticoid exposure. Doses as low as 2.5 to 7.5 mg of prednisolone equivalents per day can be associated with a 2.5-fold increase in vertebral fractures, but the risk is greater at higher doses for prolonged periods of time. The increased risk of fracture is independent of age, sex and underlying condition.

TABLE 2: ESTIMATES OF RELATIVE FRACTURE RISK AFTER 5MG PREDNISONE (OR EQUIVALENT) TREATMENT FOR 6 MONTHS

Fracture Site	Relative risk
Any	1.33 - 1.91
Hip	1.61 - 2.01
Vertebral	2.60 - 2.86
Forearm	1.09 - 1.13

DIAGNOSIS

Assessment of fracture risk with glucocorticoids is currently best performed by measurement of bone mineral density (BMD), preferably when subjects are starting glucocorticoid treatment or soon after. People receiving prednisone 5 mg per day or more should have their BMD measured at least annually for the first few years of therapy. When the BMD results are satisfactory and stable, monitoring may be less frequent.

What to do about bones in those on prednisone? ...continued

Profound changes in biochemical markers can also occur with glucocorticoids, but their use for predicting patients likely to have a fracture remains unclear and there can be wide variation between patients.

TREATMENT

There should be a holistic approach to managing elderly patients on prednisone. The main aim is to reduce fracture risk. This is done through maintaining bone mineral density while preventing additional bone loss, alleviating pain associated with existing fractures, maintaining and increasing muscle strength and initiating lifestyle changes as needed.

As the most rapid bone loss often occurs in the first 12 months after starting glucocorticoids, primary prevention in patients starting glucocorticoids, who have not yet lost bone, is the key. However, treatment (or secondary prevention) in patients already receiving long term glucocorticoid, in whom there would already be a significant degree of existing bone loss, will also be of benefit.

Important approaches to managing the bones of those on prednisone include:

- At commencement of a glucocorticoid, preventive measures need to be initiated:
  - » Smoking cessation
  - » Reducing alcohol consumption
  - » Weight-bearing and strength-building exercises
  - » Calcium intake of 1,000 to 1,500 mg per day
  - » Vitamin D 800 to 1,000 IU per day (to achieve 25 OH vitamin D level >70nmol/L)
- Use of the lowest glucocorticoid dose possible because fracture risk is dose dependent:
  - » Less than 5 mg/day prednisone equivalent result in minimal bone loss
  - » Greater than 10 mg/day prednisone will result in significant bone loss
- Use of agents that prevent or reverse bone loss:
  - » Calcitriol
  - » Bisphosphonates including alendronate, risedronate, and zoledronic acid
  - » Denosumab
  - » Teriparatide
  - » Hormone replacement therapy
  - » Raloxifene
  - » Testosterone replacement if hypogonadal
  - » Strontium

SPECIFIC AGENTS

CALCIUM AND VITAMIN D

The Cochrane Database of Systematic Reviews evaluated the data supporting the recommendation to use calcium and vitamin D as preventive therapy in patients receiving glucocorticoids. The authors concluded that because calcium and vitamin D have low toxicity and are inexpensive, all patients starting glucocorticoids should also take a vitamin D supplement prophylactically. Given the recent controversy regarding calcium supplements, calcium supplements should only be given if the patient's dietary calcium intake is inadequate.

Active vitamin D metabolites such as calcitriol (1,25-dihydroxyvitamin D) have quite distinct therapeutic effects compared with ergocalciferol or cholecalciferol (25 OH vitamin D). They have been used in glucocorticoid-induced osteoporosis largely owing to their ability to enhance calcium absorption. Although there have been a number of positive trials, other studies have shown more variable results. The conclusions have been that active vitamin D metabolites probably have a modest effect in glucocorticoid-

induced osteoporosis, but less than bisphosphonates. Serum calcium should be monitored if calcitriol is prescribed and calcium supplements should only be used if dietary calcium intake is low.

BISPHOSPHONATES

In patients already taking glucocorticoids, a bisphosphonate should be started if the bone mineral density is below a certain threshold. The rationale for using bone mineral thresholds instead of giving bisphosphonates to everyone is that these drugs have potentially significant side effects and so should only be prescribed if indicated. However, the appropriate threshold at which intervention should be considered in glucocorticoid-treated patients is controversial. Based on evidence that fractures occur at a higher bone mineral density in glucocorticoid-treated patients than in postmenopausal women, UK guidelines recommend starting a bisphosphonate if the T score is less than –1.5 at the spine or hip, but American guidelines propose a T-score cutoff of –1.0. In Australia, oral and intravenous bisphosphonates are PBS-listed for treatment of patients who are receiving prednisone ≥ 7.5 mg per day for at least three months with a BMD T-score ≤–1.5.

Whatever the BMD, its significance in terms of absolute fracture risk will differ according to the age of the patient. Therefore, use of T scores alone as an intervention threshold is not advisable and the patients overall fracture risk needs to be assessed in light of all of their risk factors. This can be ascertained using absolute fracture risk which can be estimated using fracture risk calculators such as FRAX (WHO risk calculator) or the Garvan Fracture risk calculator (www.fracturerisk calculator.com).

DENOSUMAB, AN ANTIBODY TO RANK LIGAND

Denosumab (Prolia) is a fully human monoclonal antibody to RANK ligand. Denosumab is given subcutaneously in a dosage of 60 mg every 6 months. It was recently approved for the treatment of postmenopausal osteoporosis.

TERIPARATIDE, A PARATHYROID HORMONE DRUG

Teriparatide (Forteo) consists of a fragment of the human parathyroid hormone molecule. It is given once daily by subcutaneous injection. Current PBS criteria do not include glucocorticoid induced osteoporosis. However it can be used in patients who have T scores≤-3.0 or who have fractured whilst taking bisphosphonates. Data shows increase in BMD and reduced vertebral fractures compared to standard therapy with bisphosphonates - so this is promising.

TESTOSTERONE

Due to the risk of gonadotropin and testosterone suppression with the use of glucocorticoids this may be an option for men who are found to be hypogonadal and have no contraindications to testosterone replacement. This may have the added benefit of preservation of lean body mass as well as bone mineral density. PSA should be checked prior to and during therapy.

STRONTIUM RANELATE

An oral anti-osteoporotic drug that has been shown to prevent bone loss and increased bone strength in experimental studies. At a dose of 2g/day it has been shown to increase BMD and reduce both vertebral and non vertebral fractures when given to post menopausal women. Current PBS criteria do not include glucocorticoid induced osteoporosis.

CONCLUSION

The elderly population is at high risk of falls and fractures. The addition of prednisone therapy as well as the presence of other co morbidities increases this risk further. Unfortunately, patients taking glucocorticoids are not being sufficiently educated about the risk to their bones. It is imperative that the opportunity to assess and treat these patients in the general practice setting is not missed.

KEY PRACTICE POINTS

- No oral glucocorticoid dose is safe with respect to bone, all patients starting prednisone should be evaluated
- Elderly patients are already at higher risk for falls and fractures, with the addition of prednisone this risk is increased further
- Fractures occur at higher T scores than seen in post menopausal osteoporosis, so do not wait for a drop in T score to initiate treatment
- Oral and intravenous bisphosphonates are PBS-listed for treatment of patients who are receiving prednisone ≥ 7.5 mg per day for at least three months with a BMD T-score ≤–1.5

No conflict of interest declared.

References

1. Dore RK. How to prevent glucocorticoid-induced osteoporosis. Cleveland Clinical Journal of Medicine 77(8): 529-536, 2010.
2. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporosis International 18: 1319-1328, 2007.
3. Sambrook PN. How to prevent steroid induced osteoporosis. Annals Rhematological Disease 64: 176-178, 2005.

Dr Sarah Abdo
Endocrine/Diabetes registrar St Vincent's Hospital. Bone and Calcium Registrar, St Vincent's Hospital (2010).

Dr Jerry Greenfield
Chairman, Department of Endocrinology, St. Vincent's Hospital. Deputy Director, Diabetes Centre, St. Vincent's Hospital. Conjoint Senior Lecturer, University of New South Wales. Clinical Research Fellow, Diabetes & Obesity Research Program, Garvan Institute of Medical Research.