Assessment and management of glucocorticoid-induced osteoporosis

Gerald Tracey and Tehseen Ahmed

Glucocorticoid-induced osteoporosis (GIO) is the most prevalent form of secondary osteoporosis; however, many patients taking glucocorticoids are still missing out on fracture risk assessments and bone-protection therapy. This article describes the clinical features, assessment and recommended management of GIO.

In 1932, Harvey Cushing wrote: “The greatly compressed bodies of the vertebrae... were so soft they could easily be cut with a knife.” He was, of course, describing the bones of a patient suffering from a condition that was later to be termed Cushing’s syndrome, a state of hypercortisolism.

Today, we more commonly encounter iatrogenic cases of hypercortisolism due to the widespread use of glucocorticoids. Glucocorticoid therapy is associated with many adverse effects including loss of bone density and increased fracture risk. In fact, glucocorticoid-induced osteoporosis (GIO) is the most common form of secondary osteoporosis. At any one time, approximately 1 per cent of the adult population in the UK is taking oral glucocorticoids; this figure increases to 2.4 per cent in individuals aged 70–79 years.

Pathophysiology
Bone loss in GIO is biphasic. The most rapid bone loss occurs in the first 6-12 months of glucocorticoid therapy. Bone loss then slows but continues at a rate faster than that seen with normal ageing. Glucocorticoids affect both cortical and trabecular bone although effects on trabecular bone predominate.

In the early phase of GIO, bone resorption is increased while bone formation is reduced. Glucocorticoids have indirect effects on osteoclasts, leading to enhanced osteoclast differentiation and osteoclastogenesis. Simultaneously, glucocorticoids exhibit both direct and indirect effects on osteoblasts, resulting in inhibition of osteoblast proliferation and differentiation, as well as increased apoptosis of osteoblasts.

With long-term use of glucocorticoids, osteoclast production is diminished but osteoclast survival is enhanced. Bone formation remains suppressed. This leads to an ongoing reduction in bone density.

In addition, glucocorticoids negatively affect bone via decreased calcium
absorption in the gastrointestinal tract, increased renal calcium loss, and reduced levels of sex hormones.

**Glucocorticoids and fractures**

The net result of glucocorticoid-induced effects on bone is loss of bone mass (up to 10 per cent in the first year) leading to subsequent increase in fracture risk. Fracture risk is significantly elevated even in the first few months of therapy and fractures may occur in greater than 30 per cent of patients receiving chronic glucocorticoid therapy. Fracture risk is increased for all osteoporotic fracture types and in all age groups, but fractures are more commonly seen in areas with higher proportions of trabecular bone such as the spine.

However, the increased fracture risk is unlikely to be the result of reduced bone density alone. There is an increased incidence of fracture for a given bone mineral density in GIO compared with postmenopausal osteoporosis, suggesting that bone quality is also an issue. This may, in part, be explained by glucocorticoid-induced apoptosis of osteocytes, which are thought to play an important role in determining bone strength.

A large retrospective cohort study found that the relative rate of nonvertebral fracture in glucocorticoid users vs nonuser controls was 1.33 (95 per cent confidence intervals [CI] 1.29-1.38), that of hip fracture 1.61 (CI 1.47-1.76), that of forearm fracture 1.09 (CI 1.01-1.17), and that of vertebral fracture 2.60 (CI 2.31-2.92). There does not appear to be a “safe” dosage of glucocorticoids in relation to fracture risk. Even dosages of prednisolone less than 2.5mg daily carry an increased risk of vertebral fractures. However, there is evidence of a dose-dependent relationship between chronic glucocorticoid use and fracture risk. The increased fracture risk rapidly declines after discontinuation of glucocorticoids.

**Clinical features**

In the absence of fracture, there are no particular symptoms to alert a patient to the detrimental effects of glucocorticoid on bone. Once fractures begin to occur, the symptoms and signs are the same as for any patient with osteoporosis.

Vertebral fractures, in particular, are very common (see Figure 1). They can occur early after initiation of glucocorticoid therapy and can arise without any preceding trauma. New-onset acute back pain may indicate that a fracture has occurred and warrants further investigation. Some patients will be aware of height loss and a change in posture. Again, this should alert clinicians to consider investigation to exclude vertebral fracture. Finally, a significant proportion of patients will be asymptomatic and fractures may be identified as an incidental finding on imaging studies. These patients remain at high risk of further fracture and management should be similar to patients who present with symptomatic fractures.

**Which patient groups are most susceptible?**

All patients receiving medium- to long-term systemic glucocorticoids (and those receiving frequent short courses of glucocorticoids) should be considered to be at increased risk of fracture. However, those receiving higher dosages are more at risk. Also, patients with pre-existing co-morbidities and traditional risk factors associated with poor bone health will be at greater risk of fracture (see Table 1). The effects of inhaled glucocorticoids on bone health are less certain. An increased risk of fracture has not been definitively established.

**Assessment**

An assessment of bone health should be conducted in all patients already receiving or starting systemic glucocorticoid therapy. Other risk factors and co-morbidities that may lead to compromised bone health should be sought in the history.

Laboratory investigations that should be considered include serum calcium profile and serum creatinine and electrolytes. Occasionally vitamin D testing is indicated, although for most patients a clinical evaluation to determine the likelihood of vitamin D deficiency/insufficiency should be adequate to inform management.

Fracture risk can be estimated using web-based tools such as FRAX (www.shef.ac.uk/FRAX) or QFracture (www.qfracture.org). Measurement of bone density using dual energy X-ray absorptiometry (DXA) scanning can help to refine fracture risk and can be incorporated into the FRAX calculation. Vertebral fracture assessment (VFA) can be performed at the same time as DXA scanning and involves only a small fraction of the radiation dose received with conventional spinal X-rays.

**Who to treat?**

The decision to commence bone protective therapy should be based on an assessment of fracture risk. However, the optimal risk at which intervention is indicated is not universally defined.

Pragmatically, individuals at high risk should be advised to commence bone-protective therapy at the time of starting glucocorticoids, eg those aged 65 years or over and those with a prior fragility fracture (see Figure 2).

In other patients receiving systemic glucocorticoids, in whom it is intended to continue therapy for at least three months, DXA scanning should be considered. A T score of ≤−1.5 may indicate the need for intervention with a bone-sparing agent, although the effect of age on fracture probability should be taken into account.

Alternatively, clinicians may refer to the National Osteoporosis Guideline Group (NOGG) intervention thresholds,
which can be accessed when making a calculation of fracture risk using the FRAX tool.

**Management**

**Lifestyle advice**

All patients taking glucocorticoids should receive general lifestyle advice to optimise bone health (see Table 2). It is imperative to reduce the risk of falls where applicable. The glucocorticoid dosage should be reduced where possible and consideration should be given to alternative routes of administration, e.g. inhaled, if clinically appropriate. In selected cases, steroid-sparing medications may be indicated.

**Calcium and vitamin D**

Calcium and vitamin D supplementation is important to help slow and/or prevent bone loss but there is no evidence to support a significant reduction in fractures. A recommended maintenance dose of vitamin D₃ is 800-1000IU daily and patients should be advised to aim for a total daily calcium intake of 1000-1200mg.

**Bisphosphonates**

Alendronate and risedronate are considered first-line agents for the prevention and treatment of GIO. They not only prevent bone loss but can also increase bone density in patients taking glucocorticoids. More importantly, studies have shown a trend towards a reduced incidence of vertebral fracture. Efficacy in reducing fracture at other sites is unproven.

For those patients who are intolerant or have contraindications to oral bisphosphonates, intravenous bisphosphonates may be an option. Zoledronic acid is a licensed and evidence-based therapy for GIO. In a noninferiority trial between oral risedronate and intravenous zoledronic acid (5mg once yearly), zoledronic acid was superior in terms of increasing lumbar bone mineral density. This study was not powered to show a reduction in fracture incidence.

**Teriparatide**

Teriparatide, a recombinant human parathyroid hormone given by subcutaneous injection, stimulates bone formation, increases bone mass, and reduces the risk of vertebral and nonvertebral fractures in postmenopausal osteoporosis. In the context of GIO, teriparatide has been proven to be superior to daily alendronate with significantly greater increases in bone mineral density and a
Glucocorticoid osteoporosis

The most rapid bone loss occurs early after glucocorticoid initiation and therefore all patients should undergo a fracture risk assessment at the commencement of treatment. Clinicians should be aware of the limitations of fracture risk assessment tools, which do not fully account for glucocorticoid dosage, duration or mode of delivery. Lumbar spine bone mineral density, a common site for fractures in glucocorticoid-induced osteoporosis, is not assessed with the FRAX tool. Bone mineral density is not accounted for at all with QFracture.

Alendronate, risedronate, zoledronic acid and teriparatide are all licensed for the prevention and treatment of glucocorticoid-induced osteoporosis in the UK. For patients over 65 years and/or those with a history of fragility fracture, bone protective treatment (calcium, vitamin D and an antiresorptive agent) can be considered without the need for a DXA scan.

Raloxifene has been shown to modestly increase bone mineral density at the lumbar spine and total hip compared with placebo. Raloxifene is not licensed for the treatment of GIO in the UK.

Denosumab

Denosumab is a human monoclonal antibody to the receptor activator of nuclear factor kappa B ligand (RANKL) licensed for treatment of osteoporosis in postmenopausal women and men at increased risk of fractures. It has a potent antiresorptive action and is administered subcutaneously every six months. A recent study revealed that patients who switched from oral bisphosphonates to denosumab experienced an increase in spinal bone mineral density and a decrease in bone turnover markers. It is not currently licensed for GIO but may be initiated in specialist bone clinics if licensed alternatives are unsuitable.

Duration of therapy

There is little evidence on which to base decisions about the duration of bone protective therapy in GIO. Optimisation of calcium and vitamin D status should continue for the duration of glucocorticoid therapy. Some specialists also advise continuing bisphosphonates throughout glucocorticoid therapy. However, there are already concerns about adverse effects of long-term bisphosphonates particularly with regard to osteonecrosis of the jaw and atypical femoral fractures. It is also recognised that glucocorticoid therapy itself is a risk factor for both of these adverse effects. We suggest that the role of ongoing bisphosphonate therapy should be reassessed after five years, as has been advocated in postmenopausal osteoporosis.

In those patients who discontinue glucocorticoids before five years have elapsed, a reappraisal of fracture risk should be undertaken before making decisions about discontinuation of bone protective treatment.

The GP’s role in management

Primary care teams play a central role in the assessment and management of bone health. Glucocorticoids are often initiated in primary care and patients on medium- to long-term glucocorticoid therapy can be readily identified.

Initial risk assessment and commencement of bone protective therapy can be carried out in primary care settings. Oral bisphosphonates are well understood, including the benefits and risks of treatment, and GPs are good at identifying which patients may need to be referred to secondary care for consideration of other therapies.

However, despite this, many patients are still missing out on fracture risk assessments and are not offered any bone protection therapy. It is vital that good lines of communication and treatment pathways are established between primary and secondary care if we are to reduce the impact of GIO. Finally, adherence to bone protective therapy must be monitored at regular intervals in order to ensure optimal outcomes.

References


**Further reading**

**Declaration of interests**
None to declare.

Dr Tracey is a specialist registrar in rheumatology and Dr Ahmed is a consultant rheumatologist at the Royal National Hospital for Rheumatic Diseases, Royal United Hospitals Bath NHS Foundation Trust