Glucocorticoid-induced osteoporosis: how best to avoid fractures

Mark S. Cooper

Ther Adv Chronic Dis
(2010) 1(1) 17–23
DOI: 10.1177/2040622310368737

Abstract: Glucocorticoids are one of the most commonly prescribed medications and are used to treat a wide range of chronic inflammatory diseases. The main limitation of this therapy is the development of osteoporosis and bone fractures. Recent studies have given us insight into the epidemiology of glucocorticoid-induced fractures demonstrating both the magnitude of the problem and the types of patients who are likely to be most at risk. Additionally, several randomised trials have demonstrated beneficial effects of bone targeted medications in the setting of glucocorticoid-induced osteoporosis. This article will review these recent findings, will suggest when patients are likely to be at a significant risk of fracture and discuss how best to reduce this risk.

Keywords: glucocorticoids, osteoporosis, fractures, inflammation

Correspondence to:
Dr Mark S. Cooper BM, BCh, MRCP, PhD
Clinical Senior Lecturer in Endocrinology, Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Edgbaston, Birmingham, B15 2TH, UK
m.s.cooper@bham.ac.uk

Introduction

The original description of glucocorticoid-induced osteoporosis (GIOP) was in the context of excessive endogenous production of cortisol in patients with adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas (Cushing's disease) [Cushing, 1932]. This condition is however rare and it was only when therapeutic glucocorticoids were developed and given to patients with a variety of chronic inflammatory conditions that the issue of GIOP became a widespread major medical problem. This article will examine how best to avoid the clinical endpoint of GIOP – bone fracture. This will involve understanding the epidemiology of GIOP, which sheds light on the factors that predispose to fractures in populations and individuals. It will involve trying to modify risk factors by using alternative treatments for the underlying disease where possible. Where risk is likely to remain high, attention should also be paid to maintaining and/or improving bone health through the use of bone-active medications.

Why is glucocorticoid-induced osteoporosis an important problem?

GIOP remains an important clinical problem because therapeutic glucocorticoid use is extremely widespread. Surveys in the UK suggest that approximately 1% of the adult population are taking long-term oral glucocorticoids at any moment in time [van Staa *et al*. 2000a]. Use of inhaled and topical steroids will be substantially higher than this. Glucocorticoids are used for a wide range of indications spanning almost all medical specialties. The routes of administration and the intervals between doses vary considerably. Another important factor is that the risk of fracture appears to change very quickly and substantially when using therapeutic glucocorticoids. This means that risk might be transient but any damage to the skeleton that is sustained may have a long-term adverse impact. Thus, even if the underlying disorder is cured there may be long-term effects secondary to the glucocorticoid treatment. This is an important area since there is a complex interaction with the underlying disease affecting the patient – it is hard to tell the extent to which glucocorticoids or the underlying illness are involved. Other factors make GIOP a particularly important type of secondary osteoporosis. It is a situation where bone loss can affect young people as well as the elderly.

This is also an area where some of the accepted relationships between bone density and fracture risk may not apply – the underlying pathophysiology appears to differ from that of other causes of metabolic bone disease such that clinical trial evidence for benefit of a therapeutic agent in other forms of osteoporosis may not translate directly to benefit in GIOP.

Pathophysiology of glucocorticoid-induced osteoporosis

Abnormal bone remodelling underlies most forms of metabolic bone disease. Under normal circumstances, focal areas of bone throughout the skeleton are replaced by the coordinated action of bone resorbing cells (osteoclasts) and bone forming cells (osteoblasts). Typically, an area of bone is removed by osteoclasts and a similar volume of bone is then replaced by osteoblasts. There is thus very little net change in the amount of bone lost or gained over time. With deficiency of estrogen, as occurs at the menopause, there is an increase in the activity of the osteoclasts. This leads to increased bone resorption that exceeds the amount of bone formed thus leading to net bone loss. The standard treatment for this type of bone loss is to give an antiresorbative medication which prevents the excessive osteoclastic activity and normalises bone turnover. By contrast in GIOP, the main pathophysiological mechanism appears to be an impairment of the ability of the osteoblast to form new bone [Cooper, 2004]. Bone resorption is either unchanged or accelerated but this is inappropriately high when bone formation is dramatically reduced by glucocorticoids. This therefore also leads to a net loss of bone from the skeleton but in the context of low turnover of bone. In the situation of low bone turnover there are reasons to believe that the antiresorbative medications may not be as effective as the amount of resorption is already low. The other bone cell type that appears to be very sensitive to glucocorticoids is the osteocyte [Weinstein *et al*. 1998]. Osteocytes are cells incorporated within tissue but connected to each other and surface osteoblasts through an intricate system of dendritic connections. Osteocytes are believed to be important in maintaining the viability of bone and in coordinating the repair of bone by osteoclasts and osteoblasts. Osteocytes appear to be particularly sensitive to the effects of glucocorticoids with exposure to supraphysiological levels causing these cells to undergo programmed cell death (apoptosis) [Weinstein *et al*. 1998]. This process probably underlies the development of osteonecrosis of bone (also termed avascular necrosis) in certain individuals when treated with therapeutic glucocorticoids. Glucocorticoids themselves might also have an adverse impact on the vascular supply of bone tissue further increasing the stress on osteocytes [Weinstein *et al*. 2009].

Regardless of the mechanism by which glucocorticoids affect bone tissue it is important to recognise that the adverse effects of glucocorticoids on bone metabolism are relatively reversible. The implication (supported by epidemiological data below) is that if glucocorticoids can be stopped before fractures have developed the risk of fracture should decrease substantially.

What determines the risk of glucocorticoid-induced osteoporotic fracture?

The risk of fracture in an individual can be expressed either in absolute terms or as a risk relative to individuals that are similar in some way – for example, of the same age. Relative risks are widely used to express risk reductions in clinical trials where the risk of fracture in patients treated with an active drug are compared with the risk of fracture in patients treated with a placebo. Recent epidemiological studies have provided useful data regarding both the absolute and relative risks of fracture with glucocorticoids [Vestergaard *et al*. 2005; van Staa *et al*. 2000b]. The most useful data have been derived from studies using the General Practice Research Database (GPRD). This is a database covering approximately 10% of UK primary care providers including data regarding all medications issued for these patients. This database (and others like it) has been used to assess the background risk of various types of fracture in the population as a whole and the influence glucocorticoid treatment has on this. It has also examined the dynamics of how fracture risk changes during treatment with glucocorticoids and after such treatment is stopped.

These studies reinforced the important point that background risk of fracture in the population is low in young adults of both sexes but increases rapidly from the age of around 60 in an almost exponential manner [van Staa *et al*. 2000b]. The rise in fracture risk begins earlier in women but is seen in both sexes. Glucocorticoid treatment appears to increase the risk of nonvertebral fracture in a dose-dependent manner at all ages. Doses as low as 2.5 mg prednisolone per day are associated with an increased risk [van Staa *et al.* 2000a]. The increase in relative risk appears similar across ages but since the risk of fracture rises rapidly with age the absolute increase in fracture risk is much higher in the elderly. The risk of fracture has also been quantified at the spine and hip. Risk increases in a dose dependent fashion with an approximate 5-fold increase at

the spine and a doubling at the hip. The most unexpected finding with these studies was the time course of onset and offset of fracture risk. The onset of fracture risk appeared to be very rapid with maximum risk of fracture occurring within 3 months of starting therapy. Furthermore, there is a relatively rapid offset of fracture risk with risk falling back to that of the background population within approximately 12 months [Vestergaard *et al.* 2008; van Staa *et al.* 2000b]. This surprising finding indicated that glucocorticoid effects on bone need to be considered during the early phase of treatment and this consideration should not be deferred. It also suggested that changes in bone mineral density were unlikely to be mediating these effects. Although there is a rapid decline in bone density during the first few months of glucocorticoid treatment, this decline continues subsequently at a slower rate. This gradual deterioration in bone density did not appear to influence the risk of fracture. Furthermore, it would be unlikely that an improvement in bone density could explain the relatively rapid offset of fracture risk after glucocorticoids were stopped. The reason for the rapid changes in fracture risk with glucocorticoids remains unclear but there is a degree of similarity with glucocorticoid-induced osteonecrosis (avascular necrosis) which can occur rapidly after steroids and is unrelated to bone mineral density [Weinstein *et al.* 2000].

Another important issue is the relationship between the adverse effects of glucocorticoids on bone and the impact of the underlying illness. It is likely that both of these factors make a contribution. Interestingly, children who receive large doses of glucocorticoids for the nephrotic syndrome, a condition not associated with systemic inflammation do not have significant deterioration in bone quality [Leonard *et al.* 2004]. In patients with inflammatory disease, it is possible that inflammation sensitizes bone to the effects of glucocorticoids [Hardy and Cooper, 2009]; however, an effective suppression of inflammation by glucocorticoids could lead to improved bone health by preventing the adverse effects of inflammation.

Epidemiological studies have also tried to assess the risk of fracture associated with glucocorticoids either by a non-oral route or when given intermittently. Inhaled glucocorticoid use is associated with an increase in fracture risk but it is likely that much of this risk is due to the underlying disease. This is suggested by data showing that the risk of fracture is also increased in asthmatics who are exclusively taking inhaled bronchodilators [van Staa *et al.* 2001]. The risks of direct adverse effects of therapy on bone are thought to be low with inhaled steroid use except in patients taking higher doses – for example, the equivalent of 1 mg beclomethasone or more. For patients taking intermittent glucocorticoids, the risk of fracture dose not appear to increase significantly after 1–2 short courses of glucocorticoid treatment. However, patients with a cumulative exposure to greater that 1 g prednisolone or its equivalent are at a significantly increased risk which increases further with increasing cumulative glucocorticoid exposure [De *et al.* 2007].

Although the epidemiological data are helpful in defining the overall risk in defined populations, an important feature of GIOP is that there appears to be individual factors that determine sensitivity such that some individuals are very sensitive and some resistant [Cooper, 2004]. The basis for these differences are not fully established but the activity of the glucocorticoid-metabolising enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) predicts the change in biochemical markers of bone formation in healthy volunteers treated with prednisolone [Cooper *et al.* 2003]. There is currently no clinical test that can accurately measure individual sensitivity to glucocorticoids.

How can fracture risk be reduced?

As with other forms of osteoporosis there are a range of interventions that might reduce the risk of fracture (summarised in Box 1).

Box 1. Nonpharmacological interventions to reduce risk of fracture in patients treated with glucocorticoids.

- Attempt to reduce glucocorticoid dose
- Attempt to use glucocorticoids with less systemic absorption e.g. topical/inhaled
- Try to find alternative (steroid-sparing) anti-inflammatory agent
- Encourage exercise
- Reduce risk of falls (medication review, assessment of footwear and gait)
- Ensure adequate calcium and vitamin D nutrition
- Ensure adequate lean body mass and protein/calorie nutrition
- Consider correction of hypogonadism (amenorrhoea in women, low testosterone in men)
- Consider low salt diet (to reduce urinary calcium loss).

Most nonvertebral fractures are precipitated by falls so measures to reduce falls (walking aids, appropriate footware, home assessment, medication review etc.) would appear sensible. Part of the increased risk of fractures with glucocorticoids is likely to be secondary to muscle wasting and instability resulting from glucocorticoids or the underlying disease being treated. Unfortunately, there are no data from interventional trials in this area. A critical part of trying to prevent GIOP is to effectively treat the underlying disease. This is important both to reduce the amount of glucocorticoid that the patient is exposed to and to try to reduce the damage that inflammation itself exerts on the skeleton. In many settings, biological agents are now available that have considerably reduced the inflammatory burden and allowed glucocorticoids to be reduced or stopped. Assessment by a specialist in the underlying disease would thus always seem appropriate [Cooper, 2009]. Previously, it had been argued that some therapeutic glucocorticoids were less detrimental to bone for the same anti-inflammatory potency. However, these claims have not been substantiated. Attempts to develop drugs that disassociate the beneficial effects of glucocorticoids on inflammation from the adverse effects on bone and carbohydrate metabolism are at an early stage. It is important to make sure that nutritional intake is optimal, something especially important in patients with digestive disease [Sylvester *et al.* 2007]. Low weight is a known risk factor for adverse bone health as is protein malnutrition. Adequate intakes of calcium and vitamin D are essential, especially as calcium absorption is impaired by glucocorticoids and vitamin D deficiency is common in patients with underlying illness. A diet low in sodium is recommended by some authorities as this reduces urinary calcium excretion. For many patients however these measures will be of limited use and pharmacological treatment will be required (summarised in Table 1).

Table 1. Summary of evidence supporting pharmacological treatment of glucocorticoid-induced osteoporosis.

Drug	Beneficial effect on BMD?	Reduction in vertebral fracture risk?
Calcium+/− vitamin D	No	No
Alfacalcidol	Yes[a]	Yes
Etidronate	Yes	No[b]
Alendronate	Yes	Yes
Risedronate	Yes	Yes
Zoledronic acid	Yes	Yes[c]
Teriparatide	Yes	Yes[d]

[a]effect on bone mineral density (BMD) with alfacalcidol has been shown to be less than with alendronate; [b]effect of etidronate on spine fracture risk was originally claimed to be significant but a subsequent report indicated that this effect did not achieve statistical significance; [c]for ethical reasons zoledronic acid could not be assessed relative to a placebo so was evaluated in a non-inferiority trial relative to risedronate; [d]for ethical reasons teriparatide could not be assessed relative to a placebo so was evaluated in a head to head trial with alendronate. Teriparatide had a greater effect on vertebral fracture reduction than alendronate.

Bone specific therapies

Vitamin D and vitamin D metabolites

As discussed above, adequate calcium and vitamin D intake is essential in patients taking oral glucocorticoids but there is little evidence to suggest that these nutrients alone are able to significantly reduce the risk of fracture. Their use should thus be considered as an adjunct to therapy rather than a treatment in their own right. Calcitriol and alfacalcidol are metabolites of vitamin D that have much greater biological activity than vitamin D itself. They have been used in several studies of GIOP and the data indicate that their use is associated with an increase in spine bone density and potentially a decrease in fracture risk at this site [Reginster *et al.* 1999; Ringe *et al.* 1999]. Their effect though appears to be modest and in a comparison with bisphosphonates, are much less effective in increasing bone density [de Nijs *et al.* 2006]. There remain several settings where these drugs still have a role. Bisphosphonates cannot safely be given during pregnancy or when there is significant impairment of renal function (e.g. glomerular filtration rate of <30–35 ml/min) and in these situations the active vitamin D metabolites remain a useful therapy.

Estrogens and androgens

The development of amenorrhoea or low testosterone in men is common in chronic inflammatory disease. As such it is no surprise that hypogonadism is a complicating factor in the development of GIOP. In the setting of amenorrhoea in young women and in men with symptomatic hypogonadism there will often be a case to be made for the replacement of either estrogen or androgens. However, estrogen replacement

therapy in women in the post menopausal period alone does not appear to provide sufficient protection against the development of osteoporosis and has not been evaluated in the context of a randomised trial [Lane *et al*. 1998]. The use of estrogen in this setting will be dependent on the balance of the potential benefits and risks with this type of therapy. It should be recognised that treatment with estrogen or testosterone alone will not be a sufficient treatment and there would still normally be a need for one of the therapies discussed below.

Bisphosphonates

There is now good evidence to indicate that bisphosphonates improve bone density and reduce the risk of vertebral fractures in patients taking oral glucocorticoids. This has been shown in randomised controlled trials of cyclical etidronate, alendronate and risedronate and in a non-inferiority comparison of the effectiveness of zoledronic acid relative to risedronate [Reid *et al*. 2009; Cohen *et al*. 1999; Saag *et al*. 1998; Adachi *et al*. 1997]. Although the reduction in risk of spine fractures was a secondary endpoint for these studies, the consistency of effect across studies suggests that this is a genuine effect and applies to all bisphosphonates. Bisphosphonates are generally well tolerated with their main problems being upper gastrointestinal side effects and a restriction on their use in patients with a low glomerular filtration rate. Zoledronic acid is an intravenous preparation which is free of upper gastrointestinal effects but is associated with a relatively common acute phase reaction particularly when the first dose of drug is given. Bisphosphonate usage has also been linked to the development of poorly healing lesions of the gingiva and jaw bones (osteonecrosis of the jaw) [Khosla *et al*. 2007]. The development of this complication appears to be rare in patients given the doses of bisphosphonates recommended for the treatment of GIOP. When bisphosphonates are given they are generally used for as long as the glucocorticoids are continued. Occasional case reports suggest that prolonged use of bisphosphonates, particularly in people taking glucocorticoids, can be associated with atypical fractures, particularly of the subtrochanteric region of the femur [Lenart *et al*. 2008; Odvina *et al*. 2005]. Although the absolute risk of this adverse effect appears very low, these findings do highlight the need for a careful targeting of these medications to patients who are at a significant risk of fracture.

Teriparatide

Although bisphosphonates have proved to be an effective treatment for GIOP, these drugs do not address the central pathological process involved in this condition. Whereas bisphosphonates inhibit bone resorption, the main effect of glucocorticoids is to inhibit bone formation, something that is exaggerated by bisphosphonate treatment. Teriparatide is a daily subcutaneous injection of a truncated parathyroid hormone (PTH) peptide. This treatment has an anabolic effect on bone through a stimulation of bone formation. This therapy also appears to stimulate bone formation in patients taking glucocorticoids [Lane *et al*. 1998]. In a randomised controlled trial comparing the effectiveness of teriparatide with alendronate in treating glucocorticoid-induced osteoporosis, teriparatide was found to be superior in terms of change in bone density and in the reduction of spine fractures [Saag *et al*. 2007]. Teriparatide is likely to be of most use in patients who are known to have a low bone density at the start of treatment. It is also a reasonable choice of drug in patients that have developed vertebral fractures whilst taking a bisphosphonate.

Guidelines/health economic considerations

When deciding whether to offer pharmacological treatment for GIOP an account needs to be made of the absolute benefits of therapy relative to the risk of adverse events. Patients with a very low absolute risk of fracture are unlikely to benefit from therapy but will have the same risk of adverse events as a patient at higher risk of fracture. As discussed above, epidemiological factors that increase the absolute risk of fracture include advancing age and the presence of a previous fracture. Although bone density is probably not linked closely to the relative risk of fracture when taking glucocorticoids, it is likely that a low bone density will increase the absolute risk of fracture and so should be considered a risk factor for fracture in this context. Current guidelines from the Royal College of Physicians in the UK suggest that treatment with a bisphosphonate should be given to woman and men treated continuously with oral glucocorticoids for longer than 3 months if they are over the age of 65 regardless of bone density [Compston, 2002]. In younger patients, treatment is recommended in patients who have previously had a fragility fracture or who have a bone density T-score level by dual energy X-ray absorptiometry (DXA) of less than −1.5. This threshold is derived from data from the placebo arms of the randomised

controlled trials of therapies for GIOP which indicated that younger patients that experienced a fracture generally had a bone density below this level. Overall fractures in younger men and premenopausal women were rare. Guidelines from the American College of Rheumatology suggest that patients taking prednisone doses of 5 mg or more are offered treatment with a bisphosphonate and subsequently undergo bone densitometry [American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis, 2001]. Patients with a threshold T-score of less than −1 by DXA are advised to continue bisphosphonates long term. There is thus less emphasis on patient age in the US guidelines and more emphasis on the results of bone densitometry. The introduction of the FRAX™ algorithm as a means of calculating absolute fracture risk is impacting on how osteoporosis is defined and assessed [Kanis *et al.* 2008]. The FRAX™ algorithm includes a question about glucocorticoid exposure and so could potentially help in the targeting of medications. However, this question lacks subtlety such that recent exposure is not distinguished from a trivial exposure that occurred many years earlier. As such the FRAX™ algorithm is likely to underestimate the increase in fracture risk with glucocorticoids.

No guidelines currently accommodate the use of teriparatide. The cost of teriparatide is substantially greater than that of the bisphosphonates and it is less convenient to take so it is unclear when to use teriparatide rather than a bisphosphonate. The use of the drug is likely to vary depending on local/regional health economic considerations. Situations where the benefits of teriparatide are likely to be greatest are patients who have very low bone density scores at baseline and patients that have fractures despite complying with bisphosphonate treatment.

There is even less guidance available for patients taking glucocorticoids through different routes or intermittently. As discussed above, inhaled glucocorticoids at low doses do not in themselves reduce bone density in most patients [van Staa *et al.* 2001]. Treatment (and potentially a change in therapy) should however be considered in patients that develop features of Cushing's syndrome such as weight gain, easy bruising and myopathy. Where uncertainty exists a pragmatic approach is to perform an ACTH stimulation test. Significant absorption of inhaled/topical steroids would be expected to impair the activity of the hypothalamic-pituitary-adrenal axis before there was a significant impact on bone. For patients taking intermittent glucocorticoids, there should be a low threshold for offering treatment to patients over the age of 65 (as per the RCP guidelines) if the cumulative exposure to glucocorticoids exceeds the equivalent of 1 g prednisolone [De *et al.* 2007]. An important area where bone protective therapy is usually not required is replacement corticosteroid therapy in Addison's disease or hypopituitarism. Although there has historically been chronic over-replacement in these individuals the use of lower doses of glucocorticoids should avoid any adverse effect on bones during replacement therapy.

Conclusions

Fractures associated with glucocorticoid treatment remain a common and important clinical problem. Although there are still areas which are unclear, there is fortunately now good clinical trial evidence to support the use of bisphosphonates and teriparatide in many patients treated with glucocorticoids. Due to potential adverse effects from these medications and their expense, treatment should be targeted to patients at a significant absolute risk of fracture.

Conflict of interest statement

The author has no conflicts of interest.

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