Fracture risk reduction in glucocorticoid-induced osteoporosis

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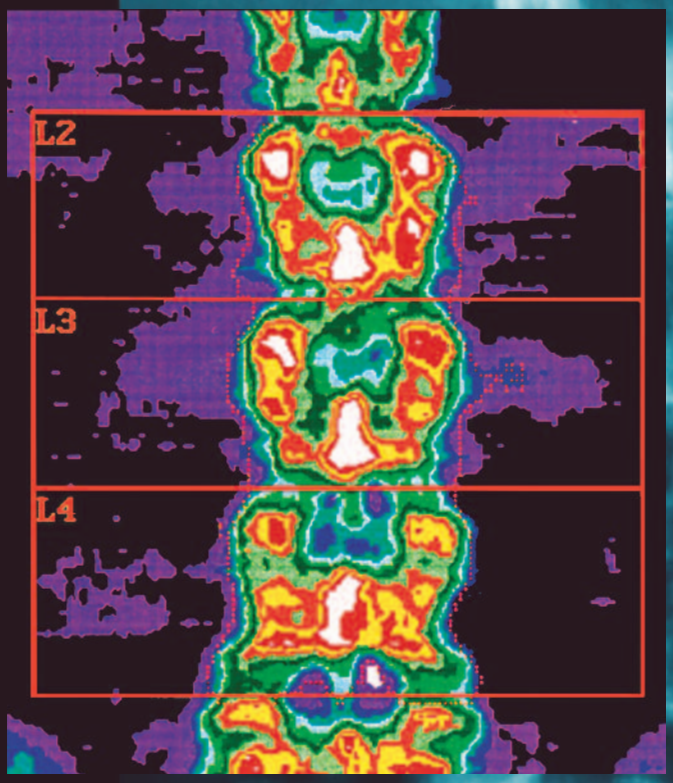
Patients requiring more than three months of glucocorticoid therapy should be assessed with regards to their fracture risk. Calcium and vitamin D supplementation is recommended as preventive therapy for all patients taking glucocorticoids, and pharmacological intervention should also be considered.



Key points

- **Glucocorticoids have many direct effects on bone cells ultimately leading to reduced formation and increased resorption.**
- **Increased risk of fracture is seen at higher bone mineral densities in patients taking glucocorticoids than those not taking glucocorticoids.**
- **Assessment of fracture risk should be considered in any patient taking glucocorticoids for more than three months.**
- **The lowest effective dose of glucocorticoids for the shortest possible time should be used.**
- **Lifestyle factors should be optimised and appropriate pharmacological intervention considered in people taking glucocorticoids.**

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Glucocorticoids are prescribed for many disorders, including autoimmune and pulmonary disorders, and after organ transplantation, making glucocorticoid-induced osteoporosis a common condition. Bone loss occurs soon after initiation of therapy. It is estimated that up to 50% of patients receiving glucocorticoids for more than six months have osteoporosis.[1] Fractures in people taking glucocorticoids occur at higher bone mineral density (BMD) than in those not taking glucocorticoids. Thus assessment of bone health should be considered in any person taking 5 mg prednisolone or more (or the equivalent) for three or more months.

Effects of glucocorticoids

Chronic use of glucocorticoids can lead to osteoporosis and fractures. The most dramatic effect of glucocorticoids on bone is due to apoptosis of osteocytes causing uncoupling of bone turnover. Glucocorticoids have many direct effects on bone cells ultimately leading to reduced formation and increased resorption (Figure).[2] Bone formation is suppressed through inhibition of osteoblast formation and increased apoptosis of osteoblasts. Increased resorption is seen as corticosteroids suppress osteoprotegerin, an inhibitor of osteoclast proliferation, and increase production of receptor activator of nuclear factor kappa-B (RANK), which is required in osteoclastogenesis.

Other negative effects of glucocorticoids on bone include inhibition of intestinal calcium absorption leading to secondary hyperparathyroidism, inhibition of gonadotrophin secretion leading to decreased oestrogen and testosterone levels, and inhibition of insulin-like growth factor-1 (IGF-1).

Rapid bone loss is seen within the first six to 12 months of therapy. With long-term use of glucocorticoids, ongoing bone loss often continues, albeit at a lower rate. Although trabecular bone is affected first so that spinal BMD decreases more than hip BMD,[3] long-term use of glucocorticoids has a severe negative impact on cortical bone loss, increasing the risk of hip fracture.

An increase in risk of fracture has been demonstrated with daily doses of glucocorticoids as low as 2.5 to 7.5 mg, and this risk increases with increasing daily dose.[1,4] The relative risks of hip and vertebral fracture after glucocorticoid therapy are 1.9 and 2.9, respectively. With glucocorticoid exposure of more than 20 months, risk of hip fracture may increase fivefold and risk of vertebral fracture 5.9-fold.[5] The increased fracture risk in patients taking glucocorticoids occurs at higher BMD than in those not taking glucocorticoids.[6] Studies have also shown an association between cumulative dose and fracture risk. Other factors, such as age, disease activity and comorbidities, may aggravate glucocorticoid-induced bone loss. Short-term use (less than three months) of glucocorticoids, is generally not thought to be harmful and fracture risk returns to baseline after cessation of glucocorticoids. Most epidemiological studies have investigated oral glucocorticoids and BMD; however, some studies suggest that inhaled corticosteroids at high doses may have detrimental effects on BMD as well.[7] The mechanisms by which corticosteroids increase fracture risk are not completely understood.[8] Possible mechanisms include qualitative and quantitative effects on bone and myopathy leading to increased risk of falls (see Figure).[2]

Assessment of fracture risk

Assessment of an individual's fracture risk is important in the management of glucocorticoid-induced osteoporosis. All risk factors should be considered, especially given that glucocorticoids increase fracture risk beyond BMD alone. A thorough history, including previous falls, fractures, other comorbidities and lifestyle factors such as smoking and alcohol intake, should be taken.

Investigations

Bone mineral density

The most common method of measuring BMD is by dual energy absorptiometry (DXA). There are a number of different DXA manufacturers (e.g. GE-Lunar, Norland and Hologic) and comparisons of actual BMD values are not valid between the different systems; although, if necessary, comparison of T-scores can provide an idea of trend. Serial BMD measurements can be used to monitor changes over time or treatment response. Ideally, measurements should be carried out on the same instrument to reduce measurement error. A DXA at 12-monthly intervals attracts a Medicare rebate for any individual taking glucocorticoid therapy.

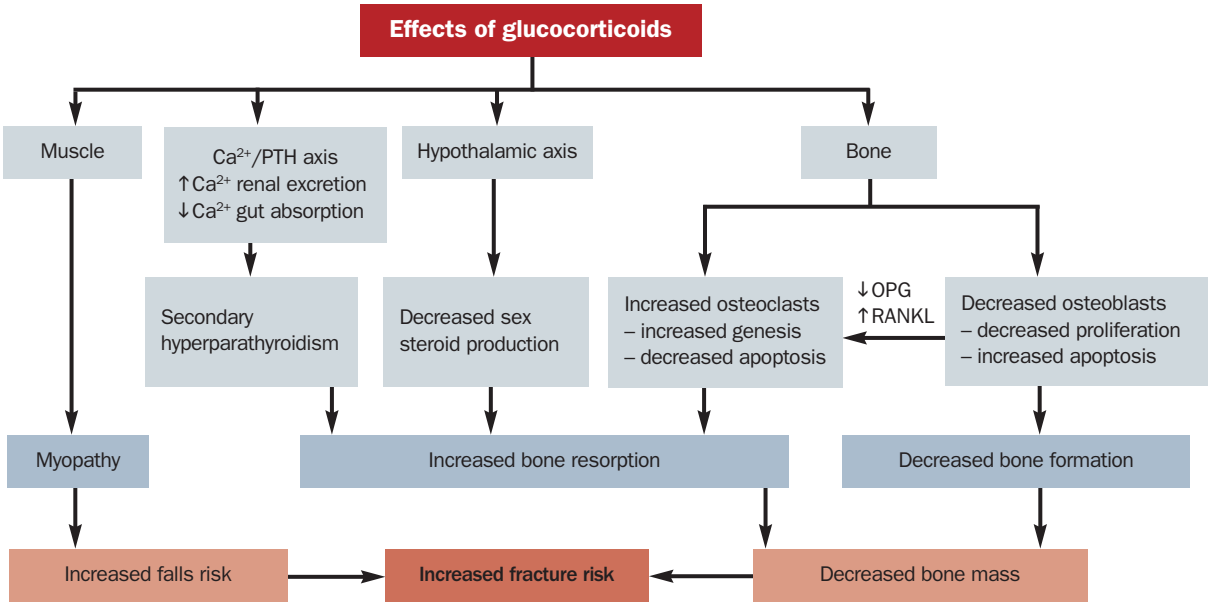

Figure. Direct and indirect effects of glucocorticoids on bone leading to glucocorticoid-induced osteoporosis and fractures.[2]

Abbreviations: OPG = osteoprotegerin; PTH = parathyroid hormone; RANKL = receptor activator of nuclear factor kappa-B.

Table. Recommended laboratory tests for glucocorticoid-induced osteoporosis

Investigation	Reason
Serum biochemistry	To exclude hyper/hypocalcaemia, renal or liver dysfunction
Serum 25-hydroxyvitamin D	To exclude vitamin D deficiency
Serum parathyroid hormone	To exclude hyperparathyroidism
Protein electrophoresis	To exclude multiple myeloma
Anti-tissue transglutaminase antibodies and IgA level	To exclude coeliac disease
Serum prolactin, oestradiol, testosterone and hormonal status	To exclude hypogonadism and/or prolactinoma if clinical suspicion

Other possible secondary causes of osteoporosis should be investigated as they may coexist with glucocorticoid-induced osteoporosis. Recommended laboratory tests are summarised in the Table.

Prevention and treatment

The lowest possible dose of corticosteroid should be used for the shortest possible time to prevent glucocorticoid-induced osteoporosis. Advice on general lifestyle factors such as smoking cessation, weight-bearing exercise and moderate alcohol consumption should be provided. Although these factors have not been studied in relation to glucocorticoid-induced osteoporosis, their deleterious effects on skeletal health are well known.

Calcium and vitamin D

All patients taking glucocorticoids should be taking 1000 to 1300 mg of calcium and 800 to 1000 IU of vitamin D daily. Data supporting the use of calcium and vitamin D supplementation as preventive therapy in patients receiving glucocorticoids have been evaluated.[9] Five trials of 274 patients with glucocorticoid-induced osteoporosis taking calcium and vitamin D supplements demonstrated a significant weighted mean difference between treatment and control groups of 2.6% in lumber spine BMD (95% confidence interval [CI]: 0.7, 4.5) and 2.5% in radial BMD (95% CI: 0.6, 4.4).[9]

Bisphosphonates

Bisphosphonates are first-line agents in preventing and treating bone loss in patients taking glucocorticoids. Bisphosphonates have been shown to reduce bone loss at the spine and femur.[10-13] However, most studies of glucocorticoid-induced osteoporosis have not been powered to study fracture as an endpoint.

Both men and postmenopausal women taking corticosteroids at a dose greater than 5 mg daily for a period of more than three months should be considered for commencing bisphosphonates. There are insufficient data in children and adolescents to recommend use of bisphosphonates widely in this population.

Alendronate and risedronate are the two oral bisphosphonates available in Australia. Zoledronic acid is a long-acting intravenous bisphosphonate that is approved as an annual infusion for glucocorticoid-induced osteoporosis. It has been shown to be non-inferior and possibly superior to risedronate in the treatment and prevention of glucocorticoid-induced osteoporosis as assessed by increases of lumbar spine BMD (least-square mean 4.06% *vs* 2.71% for treatment and 2.60% *vs* 0.64% for prevention).[14]

Calcitriol

Calcitriol (1,25-dihydroxyvitamin D_3) is an option that can be considered in young patients and/or those with mild osteopenia. Calcitriol has been shown to improve spine BMD in patients taking corticosteroid therapy.[15] It has also been shown to prevent bone loss with the initiation of high-dose corticosteroids after heart and/or lung transplantation (equivalent to the effects of bisphosphonates).[16,17] Data have been inconsistent with regards to hip BMD. Similarly, a reduction in vertebral fractures has not been consistently demonstrated in studies investigating calcitriol.[18] Serum calcium levels should be checked after commencing calcitriol because it may cause hypercalcaemia. Hypercalciuria has also been reported.

Teriparatide

Teriparatide is a recombinant form of human parathyroid hormone given as a daily subcutaneous injection. A double-blind randomised trial comparing teriparatide with alendronate in patients with glucocorticoid-induced osteoporosis showed that 18 months of teriparatide therapy (20 μg daily) increased both spine and hip BMD compared with alendronate therapy.[19] Although fracture reduction was not a primary endpoint, patients in the teriparatide group had less radiological evidence of new vertebral fractures (0.6% *vs* 6.1%; $p = 0.004$).

Denosumab

Denosumab is a fully human monoclonal antibody to the nuclear factor kB ligand. In a subgroup analysis of a 12-month randomised controlled trial of denosumab in patients with rheumatoid arthritis concurrently receiving treatment with bisphosphonates or glucocorticoids, denosumab increased mean lumbar spine and hip BMD compared with placebo regardless of concomitant bisphosphonate or glucocorticoid use.[20] Denosumab is administered as a six-monthly

Current PBS indications of therapies for glucocorticoid-induced osteoporosis

Bisphosphonates

- Osteoporosis: patients aged ≥70 years with a T-score of ≤-2.5 (alendronate) or <-3.0 (risedronate and zoledronic acid)
- Established osteoporosis: patients with fracture due to minimal trauma at any T-score
- Glucocorticoid-induced osteoporosis: patients on long-term (at least three months), high-dose (at least 7.5 mg/day prednisolone or equivalent) corticosteroids with a T-score of ≤-1.5
- For preservation of BMD in patients taking long-term glucocorticoid therapy for three months or more on a dose of 7.5 mg/day or greater of prednisolone (or equivalent) with a T-score of <-1.0 (alendronate and risedronate only)

Calcitriol

- Hypocalcaemia due to renal disease
- Hypoparathyroidisim
- Hypophosphataemic rickets
- Vitamin D-resistant rickets
- Established osteoporosis in patients with fracture due to minimal trauma
- No PBS indication for glucocorticoid-induced osteoporosis

Teriparatide

- Severe established osteoporosis: patients with established osteoporosis and a T-score of ≤-3.0 and two or more fractures due to minimal trauma and have experienced at least one symptomatic new fracture after at least one year of continuous antiresorptive agent at adequate doses (and can only be initiated by specialists)
- No PBS indication for glucocorticoid-induced osteoporosis

Denosumab

- Osteoporosis: women aged ≥70 years with a T-score of ≤-2.5
- Established postmenopausal osteoporosis: in patients with minimal trauma fractures at any T-score
- Not approved by the TGA for glucocorticoid-induced osteoporosis

Strontium ranelate

- Osteoporosis: women aged ≥70 years with a T-score of ≤-3.0
- Established postmenopausal osteoporosis: patients with fracture due to minimal trauma at any T-score
- Note: there are no studies of strontium ranelate use in glucocorticoid-induced osteoporosis and it is not approved by the TGA for this indication

subcutaneous injection. It has been shown to be effective in the treatment of osteoporosis; however, it is only currently PBS listed for use in postmenopausal women (the box above lists the PBS indications of therapies for glucocorticoid-induced osteoporosis). Denosumab is not approved by the TGA for glucocorticoid-induced osteoporosis.

Conclusion

Glucocorticoids are widely prescribed for their anti-inflammatory properties. Glucocorticoid-induced bone loss can occur at doses as low as 2.5 mg. Rapid bone loss through suppression of bone formation and increased resorption occurs within six to 12 months of glucocorticoid therapy. Patients requiring more than three months of glucocorticoid therapy should be assessed with regards to their fracture risk. Calcium and vitamin D supplementation is recommended as preventive therapy for all patients receiving glucocorticoids. Pharmacological intervention should also be considered. **ET**

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COMPETING INTERESTS: Dr Chen: None. Associate Professor Center has received honoraria for educational talks conducted by Merck Sharp and Dohme, Amgen, Sanofi Aventis and Novartis.