Steroid-induced osteoporosis: how can it be avoided?

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Clinical significance of steroid-induced osteoporosis

In 1932, Harvey Cushing wrote: ‘The greatly compressed bodies of the vertebrae ... were so soft they could easily be cut with a knife’. Today, steroid-induced osteoporosis is still of major clinical relevance. Glucocorticosteroids induce a biphasic bone loss with a rapid initial phase of \( \sim 10-15\% \) during the first few months and a slower phase of \( \sim 2-5\% \) annually. As shown in Figure 1, steroids do not only reduce the lifespan and promote the apoptosis of osteoblasts and osteoclasts but also decrease the recruitment of osteoblasts and osteoclasts from progenitor cells [1]. Apoptosis and changes in the expression of bone growth factors contribute to a decline in bone formation and the occurrence of osteonecrosis.

Steroid therapy affects particularly the axial skeleton and the proximal femur. The earliest changes of steroid-induced bone loss can be detected in the lumbar spine (preferably lateral position). During long-term (\( >3 \) month) use of steroids (\( >7.5 \) mg prednisone) bone loss occurs in \( \sim 50\% \) of patients, osteoporotic...
fractures in 25% of patients and osteonecrosis in some patients. Based on data in 244,235 patients and in 244,235 controls, with daily prednisone doses between 2.5 and 7.5 mg, the risk of fracture is 1.77 (CI 1.55–2.02), and the risk is 2.27 with doses >7.5 mg (CI 1.94–2.66) [2]. Inhaled steroids also cause significant bone loss [3]. In up to 50% of kidney transplantation patients, steroids induce alterations in bone architecture leading to a decline in bone mineral density and progressive vertebral height loss [4]. Risk factors for steroid-induced bone loss are diminished bone mass, vitamin D deficiency, hyperparathyroidism, negative calcium balance, chronic renal failure, metabolic acidosis, suppressed osteoblast function and malnutrition.

Prevention and treatment of steroid-induced osteoporosis

Although there are effective drugs to avoid steroid-induced osteoporosis the percentage of patients receiving therapy to prevent bone loss ranges from 14% (e.g. UK) to 51% (e.g. Iceland) [5].

The goals in the management of steroid-induced osteoporosis are: (i) to maintain current bone mass and to prevent additional bone loss; (ii) to alleviate pain associated with existing fracture(s); (iii) to maintain/increase muscle strength; and (iv) to initiate lifestyle changes as needed.

Baseline therapy comprises physical activity (skeletal loading), dietary control of calcium and phosphate intake and avoidance of smoking and excessive alcohol intake. Sodium restriction and thiazide diuretics have been shown to improve gastrointestinal absorption and to decrease urinary excretion of calcium [6]. Patients who excrete >300 mg of calcium/24 h may benefit from a low-dose thiazide diuretic (e.g. hydrochlorothiazide 12.5–25 mg/day).

The recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis given by the 2001 update of the American College of Rheumatology [7] are shown in Table 1.

Calcium and vitamin D

Deficiency in calcium and vitamin D is a major risk factor for bone loss. Vitamin D plus calcium is superior to no therapy or calcium alone and should be given as baseline therapy to prevent or treat steroid-induced osteoporosis [6-9]. Vitamin D (500–1000 IU/day) and calcium (500–1000 mg/day) given for 2 years significantly prevented bone loss at the lumbar spine and forearm but did not influence fracture incidence, femoral neck bone mass or markers of bone resorption [10].
Patients who are hypogonadal treatment in all men and postmenopausal women receiving medium to high dose glucocorticoid therapy. This can be prevented by substitution with low calcitriol levels contributing to secondary hyperparathyroidism. In renal failure, diminished serum calcium absorption from the gut and mineralization of vitamin D metabolites (alfacalcidol, calcitriol) optimize Active vitamin D metabolites. Steroids inhibit calcitriol synthesis and modify vitamin D effects on osteoblasts. Active (1α-hydroxylated) vitamin D metabolites (alfacalcidol, calcitriol) optimize calcium absorption from the gut and mineralization of the bone matrix [11]. In renal failure, diminished serum calcitriol levels contribute to secondary hyperparathyroidism. This can be prevented by substitution with low doses of alfacalcidol or calcitriol [12,13]. In 85 patients on long-term steroid therapy receiving 1.0 μg alfacalcidol plus 500 mg calcium daily or 1000 IU vitamin D3 plus 500 mg calcium daily, alfacalcidol significantly increased bone mineral density at the lumbar spine and reduced the rate of vertebral fractures from 21 in 17 patients (placebo) to 12 in 10 patients (alfacalcidol; P<0.0001) [14]. In a randomized, placebo-controlled clinical trial, 145 steroid-naive patients (among them 20% with systemic lupus erythematosus) received alfacalcidol (1.0 μg/day) or placebo. As shown in Figure 2, in this study alfacalcidol significantly prevented bone loss from lumbar spine induced by prednisolone (mean dose 46 mg/day) [15].

Bisphosphonates

Several large randomized controlled clinical trials provide evidence that etidronate, risedronate and alendronate are effective in the prevention and treatment of steroid-induced osteoporosis [7,9,10,16]. In 141 patients, intermittent cyclic therapy with etidronate or placebo for 1 year (400 mg/day, for 14 days, followed by 76 days of supplementation with 500 mg calcium/day) prevented steroid-induced bone loss and reduced the number of fractures from 22 in 10 patients (15.4%; placebo group) to 5 in 5 patients (8.8%; etidronate group) [17]. These findings were supported by a larger trial in 477 subjects receiving placebo or alendronate at 5 or 10 mg [9]. In kidney transplanted patients, the bone fracture rate increased 5-fold after transplantation and correlated significantly with the steroid dose [18]. In these patients, bisphosphonates (e.g. pamidronate) are superior to calcitonin or calcium in prevention of steroid-induced bone loss without an adverse impact on graft function [19]. A recent study compared the protective effect of calcitriol (0.5 μg/day, for 6 months) or etidronate (two cycles plus calcium) on bone loss after cardiac or lung transplantation in 41 patients. Bone loss was significant despite prophylaxis with either agent and did not differ between groups at 6 and 12 months [20]. Taken together, bisphosphonates are as effective as active vitamin D metabolites, but more effective than native vitamin D and/or calcium alone [7,9,21].

Hormone replacement therapy

The inhibition of bone formation during steroid therapy is due, at least in part, to suppression of adrenal androgen secretion (Figure 1). Postmenopausal women, premenopausal women with menstrual irregularities and patients with hypogonadism should receive hormone replacement therapy. Premenopausal women should be offered oral contraceptives. In men with hypogonadism, testosterone therapy is effective. For postmenopausal women conjugated oestrogens (e.g. oestrogen patch) are the first choice. In postmenopausal women, it appears that oestrogens should be given for at least 7 years to prevent bone loss [22]. On the other hand, there is evidence that 5 years of oestrogen therapy increases the risk of breast cancer by 20–50%.

Calcitonin and fluorides

In the prevention of steroid-induced osteoporosis, calcitonin is not more effective than native vitamin D and less effective than bisphosphonates [6,7,21]. Fluorides selectively increase the density of trabecular bone, which could be particularly attractive for the therapy of steroid-induced osteoporosis. However, there is no convincing data with fluorides in this condition. Moreover, there are concerns about

Table 1. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update of the American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis

<table>
<thead>
<tr>
<th>Prevention and treatment in all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplementation of calcium and vitamin D (800 IU/day) or activated vitamin D (e.g. alfacalcidol 1 μg/day or calcitriol 0.5 μg/day)</td>
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<tr>
<th>Patients receiving medium to high dose glucocorticoid therapy</th>
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<tr>
<td>Supplementation of calcium and activated vitamin D (e.g. alfacalcidol 1 μg/day or calcitriol 0.5 μg/day)</td>
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<tr>
<th>Treatment in all men and postmenopausal women</th>
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<tr>
<td>Bisphosphonates (e.g. etidronate)</td>
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<th>Patients who are hypogonadal</th>
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<td>Hormone replacement therapy (e.g. oestrogen or testosterone)</td>
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Fig. 2. Alfacalcidol significantly prevents steroid-induced bone loss from lumbar spine (BMD, bone mineral density). Data from Reginster et al. [15].
potential harmful effects on bone quality, because high cumulative doses of fluorides induce an osteomalacia-like condition, called fluorosis.

Summary

Patients who will remain on glucocorticoids for more than a few weeks are clearly at risk for osteoporosis. Steroid-induced bone loss should be prevented, and if present, should be treated. Exercise programmes and the maintenance of a good nutritional status with an adequate calcium and phosphate intake and a restricted sodium intake are recommended. Supplementation with calcium and vitamin D should be given to all patients to restore normal calcium balance. Hormone replacement therapy should be considered in amenorrheic women. Patients with medium- to high-dose steroid therapy should receive bisphosphonates or an activated form of vitamin D. Therapies should be continued as long as the patients are on steroids. To ensure that prevention of steroid-induced osteoporosis is developing as the standard of care for patients receiving long-term steroid treatment, a broad educational effort directed to physicians of various specialties is needed [23].

Note added in proof

Recently published studies on hormone replacement therapy in women with osteoporosis who have severe vascular disease report significant adverse effects with special regard to cardiovascular outcome. Based on current studies, treatment with parathyroid hormone increases vertebral bone density in postmenopausal women with steroid-induced osteoporosis.

References