

Steroid-induced Osteoporosis

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Abstract

Introduction: Corticosteroids have major effects on calcium metabolism, leading to accelerated osteoporosis and fracture. **Methods:** This review will attempt to summarise current knowledge about their effects in light of new information and important remaining questions, especially with respect to management of this common condition. **Results:** Corticosteroids affect bone through multiple pathways, influencing both bone formation and bone resorption. Evidence from randomised trials suggests that postmenopausal women receiving corticosteroids are at greatest risk of rapid bone loss and consequent fracture and should be actively considered for prophylaxis. Based upon available evidence, the rank order of choice for prophylaxis would be a bisphosphonate followed by a vitamin D metabolite or hormone replacement. **Conclusions:** With early therapy, corticosteroid bone loss can be effectively prevented or reversed.

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Mechanisms of Corticosteroid Bone Loss

Corticosteroids are known to affect bone through multiple pathways (Fig. 1), influencing both bone formation and bone resorption, and these mechanisms have been reviewed.¹⁻³ The most important effects appear to be on bone formation due to direct effects on cells of the osteoblastic lineage⁴ although indirect effects related to sex steroid production are also important. Although biphasic effects on osteoblasts have been observed in organ culture,⁵ the predominant effect of corticosteroids is inhibitory towards osteoblasts and differentiation of osteoblast precursors, with studies also showing corticosteroids can decrease levels of mRNA encoding for osteoblast products such as osteocalcin.⁶ Increased osteocyte apoptosis has also been implicated as an important mechanism of corticosteroid osteoporosis.⁵ Corticosteroids have been shown to reduce the birth rate of osteoblasts and osteoclasts and cause earlier death of osteoblasts.⁷ The effect of glucocorticoids to promote apoptosis in osteocytes as well as in osteoblasts could account for the increase in fracture susceptibility. Corticosteroids have been shown to decrease intestinal calcium absorption of calcium in balance studies and using radioisotopic techniques⁸ and increase urinary phosphate and calcium loss by direct effects on the kidney,⁹ contributing to secondary hyperparathyroidism⁹ and hence increased bone resorption. At the organ level, direct inhibitory effects of corticosteroids on bone formation

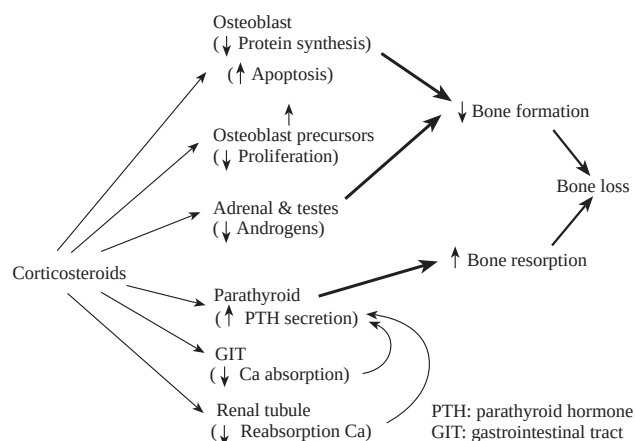


Fig. 1. Schematic diagram of effects of corticosteroids on bone metabolism. The thicker arrows for effects on bone formation indicate this is more important than effects on bone resorption.

have also been documented in histomorphometric studies.¹⁰ It is likely that the early transient enhanced activation frequency of bone remodelling units, due to secondary hyperparathyroidism, together with inadequate new bone synthesis, due to suppression of osteoblastic function, results in net bone loss with corticosteroids (Fig. 2).

Corticosteroids and Fractures

The major clinical manifestation of the effects of corticosteroids on bone are fractures most commonly in the

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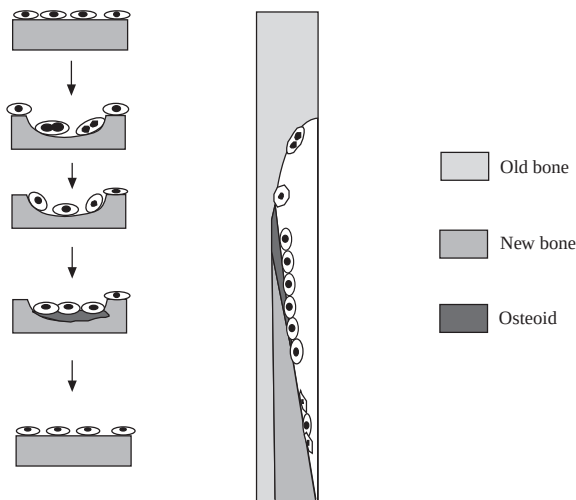


Fig. 2. Schematic diagram of the bone remodelling cycle. A trabecular BMU is depicted in a longitudinal section down the page (right panel) and at selected transverse sections (left panels). Successive stages of quiescence, activation, resorption, formation and quiescence occur. Corticosteroids may enhance activation early but later delay the interval between completion of resorption and onset of formation due to enhanced osteoclast and osteoblast apoptosis.

vertebrae and ribs, regions of the skeleton with high amounts of trabecular bone. In an early study of corticosteroid dependent asthmatics, 11% of 128 patients surveyed had sustained 58 fractures and 42% of 19 patients (mean duration of corticosteroid use 8 years) followed prospectively sustained fractures, predominantly vertebral and to a lesser extent ribs.¹¹ Two studies have suggested that corticosteroid-treated patients suffer vertebral fractures at higher threshold levels of spinal bone density than observed in involutional osteoporosis, suggesting a qualitative as well as quantitative defect of bone,^{12,13} although another study found no such evidence.¹⁴ Another study of multiple sclerosis patients treated with corticosteroid reported fractures in 19% of 103 patients although the relatively high incidence of limb fractures appeared to reflect falls due to worsening multiple sclerosis.¹⁵

The prevalence of vertebral fracture with corticosteroids is about 28%.¹⁶ A large cohort study of subjects on corticosteroid, identified from a general practice registry in the United Kingdom, observed that the relative risk of clinical vertebral fracture during oral corticosteroid therapy was 2.6, with the relative risk for hip fracture and for non-vertebral fracture being 1.6 and 1.3, respectively.¹⁷ Fracture risk increased with increasing daily doses of corticosteroids and when discontinued, the fracture risk appeared to return to baseline.

Which Patients Lose Bone with Corticosteroids at Which Sites

When high-dose corticosteroids are used, bone loss can be rapid ranging between 5% and 15% per annum.^{18,19} However, not all patients on corticosteroids lose bone. The

reasons for this large degree of individual variation are unknown but probably include differences in dose, underlying disease and genetic susceptibility to corticosteroids. Another possibility is variability in the pharmacokinetics of corticosteroids between individuals which have not been adequately studied.²⁰

Bone loss with corticosteroids is most rapid in the first 12 to 18 months after starting therapy, followed by a slower decline in patients on chronic glucocorticoids. In a serial histomorphometric study, treatment with prednisone (10 to 25 mg/day) resulted in a 27.1% decrease in iliac crest cancellous bone volume by 6 months; however, no further decline was observed at re-biopsy after 19 months.²¹

As noted above, corticosteroid bone loss is dose dependent,¹⁷ although "low-dose" corticosteroids may still cause rapid initial bone loss in some patients. In patients on chronic low-dose therapy, it is uncertain whether there is continuing slow loss, although the few longitudinal studies and clinical trials suggest it may stabilise in some individuals.²²⁻²⁴ Studies in Addison's disease have found no significant reductions in forearm bone density in men or premenopausal women receiving replacement doses of cortisone acetate between 25 and 37.5 mg daily.²⁵ Gough et al²⁶ reported that spinal bone loss in rheumatoid arthritis was related to disease activity and observed greater loss in patients treated with daily prednisolone doses ranging between 1 and 5 mg than doses of more than 5 mg because of poorer disease control in the former group.

Inhaled steroids are less likely to have systemic effects than oral corticosteroids, but in higher doses result in adrenal suppression and reduced bone density. Analysis of inhaled corticosteroid users from the general practice registry in the United Kingdom matched against controls observed the relative risk of vertebral, hip and non-vertebral fracture was 1.5, 1.2 and 1.2, respectively, but no differences were found between the inhaled and bronchodilator groups.²⁷ The benefit of flixatide over other inhaled steroids is unclear.²⁸

The degree of bone loss due to corticosteroids varies markedly according to skeletal site. For example, in one study of 17 patients with chronic corticosteroid excess, mean bone density was reduced to -1.94 standard deviations at the lumbar spine compared to -0.33 standard deviations in the distal radius and +0.29 in the midradius.²⁹ But although trabecular bone has been considered to be more susceptible than cortical bone, it is recognised that corticosteroids affect some cortical sites, such as the neck of femur, as much as the trabecular bone sites.³⁰ These differences are reflected in fracture rates at different sites.¹⁷

Biochemical Markers of Corticosteroid Bone Loss

The complex effects of corticosteroids on bone are

reflected in marked changes in biochemical markers of bone turnover, opening the possibility that some combination of markers may be predictive of those patients who lose bone with corticosteroids. Markers of bone formation, such as serum osteocalcin, fall within hours of treatment with corticosteroids to as low as 30% of their pre-treatment level.⁹ Osteocalcin levels gradually recover towards pre-treatment values as corticosteroid doses are reduced over time^{31,32} and are significantly related to corticosteroid dose.³³ However, whilst many studies have shown a marked decline in such markers after corticosteroid use, no studies have shown the degree of suppression to be predictive of bone loss.

Older markers of bone resorption have generally not been found to be markedly elevated in corticosteroid-treated patients except in those with spinal fractures³⁴ or airways disease.³⁵ Newer, more sensitive markers of bone resorption have been shown to rise following acute corticosteroid administration.^{9,36}

Corticosteroids also have profound effects on sex steroids. Thus, in males treated with corticosteroids, low serum testosterone levels have been reported³⁷ and in females low adrenal androgens.³⁸

Treatment of Corticosteroid Bone Loss

Over the last 10 years there have been an increasing number of studies investigating the efficacy of various treatments in corticosteroid bone loss. As bone loss is most rapid soon after starting corticosteroids, the studies are best classified as either primary prevention (in patients starting corticosteroids) or treatment of established loss (in patients on chronic therapy).

To summarise, evidence from recent trials suggests that postmenopausal women receiving corticosteroids are at greatest risk of rapid bone loss and consequent fracture and should be actively considered for prophylactic measures. In men and premenopausal women receiving corticosteroids, the decision to use prophylaxis is less clear and will depend upon a number of factors including bone mineral density (BMD), anticipated dose and duration of corticosteroids and other risk factors. Based upon available evidence, the rank order of choice for prophylaxis would be a bisphosphonate followed by a vitamin D metabolite or an oestrogen-type medication. Since fracture risk is a function of multiple factors including the severity of low bone density as well as the duration of exposure, treatment with therapy to increase bone density will further reduce fracture risk in patients receiving chronic low-dose corticosteroids.

Hormone therapy is frequently recommended for corticosteroid-treated patients, but the evidence supporting its use is limited. In women, there has also been only one

randomised controlled trial of the effect of oestrogen on disease activity and bone loss in rheumatoid arthritis.³⁹ In a small subgroup of patients who were receiving chronic low-dose corticosteroids, lumbar BMD increased by 3.8% over 2 years compared to 0.6% loss in the calcium-treated control group. In men, there has been only one trial in 15 asthmatic men receiving chronic corticosteroids comparing testosterone 250 mg/month with calcium 1000 mg in a crossover design. After 12 months, testosterone increased lumbar BMD by 5%, which was significant compared to calcium, but the calcium group had no significant loss.⁴⁰ No fracture data are available from any of these studies.

Several trials have examined the efficacy of bisphosphonates on corticosteroid-induced bone loss and vertebral fractures. Adachi et al⁴¹ studied 141 patients initiating corticosteroids who received prophylaxis with either cyclical etidronate or 500 mg of calcium. At the end of 1 year, mean lumbar BMD change with etidronate was +0.6 % compared to -3.2 % in the calcium group. For postmenopausal women only, there was a significant difference in the incidence of new vertebral fractures determined semi-quantitatively, favouring etidronate (21.9% versus 3.2%). There are a few features about this study that need to be considered in interpreting its results. Firstly, baseline lumbar spine BMD in the postmenopausal women was about 1 SD lower in the control group, which could be expected to double their fracture risk. Secondly, the etidronate group included a significantly greater number of patients with rheumatoid arthritis than the control group which is an independent risk factor for osteoporotic fracture.

Saag et al²³ reported the combined results of two trials in 477 corticosteroid-treated subjects who received prophylaxis with alendronate or calcium/vitamin D (800 to 1000 mg daily plus 250 to 500 IU daily, respectively). Patients were stratified according to whether they had received corticosteroids for <4 months, 4 to 12 months or >12 months. Over 12 months of follow-up, the mean change in lumbar spine BMD in patients in the primary prevention group was +3.0% for alendronate 10 mg/day compared to -1% in the placebo group. In those who had received chronic corticosteroids for >12 months, the increase with alendronate was +2.8% but also +0.2% for calcium. The relatively minor spinal bone loss seen in patients enrolled within 4 months of initiating corticosteroids and treated with calcium/vitamin D (-1%/year) contrast with the findings of the only study with a true (untreated) control group,⁴² in which cumulative doses of corticosteroids were higher and spinal bone loss averaged 4% to 5%/year despite treatment with calcium with vitamin D. A posthoc analysis of incident vertebral fractures determined semi-quantitatively significantly favoured alendronate in

postmenopausal women only (13% versus 4.4%).

Risedronate has also been examined in corticosteroid osteoporosis.⁴³ In a primary prevention trial in 224 corticosteroid-treated subjects who received prophylaxis with either risedronate or calcium 500 mg daily, risedronate 5 mg per day prevented spinal bone loss (+0.6%) compared to calcium (-2.8%) over 12 months. Incident vertebral fracture rates were 17.3% with calcium and 5.7% for risedronate 5 mg ($P = 0.072$). Vertebral fractures were only seen in postmenopausal women and men, not in premenopausal women. In 290 patients receiving chronic corticosteroid treatment (prednisone ≥ 7.5 mg/day for ≥ 6 months), treatment with risedronate in a dose of 5 mg significantly increased lumbar spine (+2.9%) and femoral neck (+1.8%) BMD. Treatment with risedronate 2.5 mg daily showed a similar, although non-significant trend. Although not powered to show fracture efficacy, 15% of patients in the control group versus 5% in the risedronate group sustained new vertebral fractures suggesting a 70% reduction in fracture rate.

Calcium is often used alone or in combination with vitamin D in corticosteroid osteoporosis based upon studies in the 1970s that measured only forearm BMD.⁴⁴ Since bone density was only measured in the radius, whereas most of the bone loss occurs from the spine with corticosteroids, the clinical significance of these findings is unclear. The only primary prevention study of calcium and vitamin D with lumbar bone density as a primary endpoint is the study by Adachi et al⁴² which compared combination calcium/vitamin D (1000 mg daily plus 50,000 units weekly, respectively) against placebo over 3 years in 62 patients starting corticosteroids. Bone loss at the lumbar spine was not significantly different between calcium/vitamin D and placebo and the amount of bone loss observed over 1 year with the calcium/vitamin D combination (4.9%) was similar to that seen in the calcium alone treated control groups in other prevention studies.⁴³ However, a secondary prevention study by Buckley et al²² in 65 patients receiving chronic low-dose corticosteroids for rheumatoid arthritis observed an annual spinal loss of 2.0% in placebo-treated patients compared to 0.7% gain in calcium/vitamin D₃-treated patients (1000 mg plus 500 IU/day, respectively). As the patients were on chronic low-dose corticosteroid, the BMD rise may have been a "remodelling transient" and the results are not necessarily applicable to patients commencing high-dose corticosteroids.

Although the term vitamin D is sometimes used to encompass both the calciferols and active vitamin D metabolites, they have quite distinct therapeutic effects. The most commonly used active hormonal forms of vitamin D are calcitriol (1,25 dihydroxy vitamin D) and alfacalcidol (1 α hydroxy vitamin D). Two studies have examined their

use in primary prevention of corticosteroid osteoporosis. Sambrook et al⁴⁵ examined the effect of 12 months of calcium, calcitriol or calcitonin in 103 patients starting corticosteroids. Patients treated with calcium lost bone rapidly at the lumbar spine (-4.3%/year) whereas patients treated with calcitriol lost at a much reduced rate (-1.3%/year). A randomised, double blind, controlled trial in 145 patients starting corticosteroids compared alfacalcidol with calcium.⁴⁶ After 12 months, the change in spinal BMD with alfacalcidol was +0.4% compared to -5.7% with calcium. The exact mechanism of this apparent benefit of active metabolites compared to simple vitamin D for primary prevention is unclear, but may relate to reversal of early secondary hyperparathyroidism. Calcitonin has been studied in patients starting corticosteroids and receiving chronic corticosteroids with variable results⁴⁷ and its efficacy remains unproven.

With regard to other agents, Lane et al⁴⁸ performed a randomised, controlled trial of parathyroid hormone (PTH) in oestrogen-treated postmenopausal women with corticosteroid osteoporosis. The patients treated with human parathyroid hormone (hPTH) and hormone replacement therapy (HRT) had significant increases in bone density (+11% by lumbar spine 1% hip) after 1 year and essentially no changes were observed in the oestrogen control group. The treatment with PTH resulted in a dramatic increase in the biochemical markers of bone turnover. Bone formation, measured by osteocalcin, increased more than 150% above baseline levels within 1 month of starting the therapy and remained elevated for the remainder of the treatment period. Bone resorption, measured with deoxypyridinoline cross-links increased to the same levels as the bone formation marker, but this required 6 months of therapy.⁴⁸ The study was not powered to determine if PTH could reduce new vertebral fractures but results from a recent study in postmenopausal women was encouraging in this regard.⁴⁹

Summary

Corticosteroids have major effects on calcium metabolism, leading to accelerated osteoporosis and fracture. Corticosteroids affect bone through multiple pathways, influencing both bone formation and bone resorption. Evidence from randomised trials suggests that postmenopausal women receiving corticosteroids are at greatest risk of rapid bone loss and consequent fracture and should be actively considered for prophylaxis. Based upon available evidence, the first choice for prophylaxis should be a potent bisphosphonate followed by a vitamin D metabolite. Hormone replacement therapy should be considered if hypogonadism is present. With early therapy, corticosteroid bone loss can be effectively prevented or reversed.

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