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REVIEW

Management of corticosteroid-induced osteoporosis

RICHARD EASTELL, on behalf of a UK Consensus Group Meeting on Osteoporosis*
From the Department of Human Metabolism and Clinical Biochemistry, University of Sheffield, Sheffield, UK

Abstract. Eastell R, on behalf of a UK Consensus Group Meeting on Osteoporosis (Department of Human Metabolism and Clinical Biochemistry, University of Sheffield, Sheffield, UK). Management of corticosteroid-induced osteoporosis (Review). *J Intern Med* 1995; 237: 439–47.

Corticosteroid therapy results in osteoporosis. There is a doubling in the risk of fracture in patients taking more than the equivalent of 7.5 mg day^{-1}. The bone loss is most rapid from the axial skeleton, particularly during the 1st year of therapy. The most important mechanism for the bone loss is a decrease in osteoblastic activity. Preventative strategies should be targeted to patients with low bone-mineral density, especially if the dose of corticosteroids is likely to be high. Treatment strategies agreed on by the Consensus Panel included hormone replacement therapy and bisphosphonates, with monitoring of efficacy by bone densitometry.

Introduction

All physicians are aware that osteoporosis is one of the major complications of corticosteroid therapy. However, the literature on this topic is very difficult to interpret because the effects of corticosteroids are dose-dependent and because the disorders for which these agents are given may affect bone. The following review summarizes a meeting held to try to resolve these issues by a group of clinical investigators from the UK. The meeting was timely in that, in the past 12 months, a number of reports have been published on the primary prevention of corticosteroid-induced osteoporosis (CSIO).

The scope of the problem

The association of osteoporosis and corticosteroids was made shortly after the first use of these drugs in humans in the 1950s. It was particularly highlighted in patients treated for asthma [1]. The first population-based study of limb fractures was by Hooyman *et al.* who reported that the relative risk of hip, distal forearm, and proximal humerus fractures was doubled in a group of patients with rheumatoid arthritis treated with corticosteroids compared to patients with rheumatoid arthritis alone [2]. A subsequent British study has confirmed that use of corticosteroids leads to an approximate doubling of hip fracture risk [3]. Both Hahn *et al.* and Verstraeten *et al.* reported a four- to five-fold increase in vertebral fracture prevalence in groups of patients with rheumatoid arthritis treated with corticosteroids compared to patients with rheumatoid arthritis alone [4, 5], although this was not found by Spector *et al.* using a morphometric approach to defining fractures [6]. Such studies may be criticized in that steroids were used in patients with more active rheumatoid arthritis, as assessed by the erythrocyte sedimen-

* Participants at the Consensus Meeting were: Cyrus Cooper, Roger Francis, David Hosking, David Purdie, Jonathan Reeve, David Reid, Graham Russell and John Stevenson.

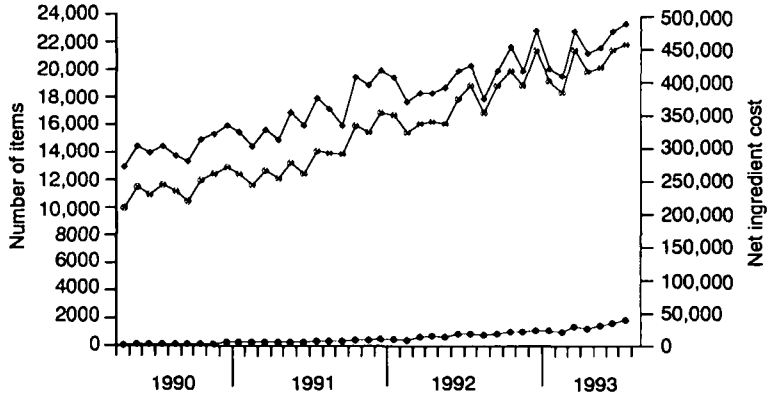

Fig. 1 Prescribing patterns for glucocorticoids in respiratory diseases in Hampshire, UK, between 1990 and 1993. Symbols represent the cost (○) in pounds sterling (right hand axis), and the number of items (◆), and generic items (●). (Data from the Hampshire FHSA and Prescription Pricing Authority, 1993.)

tation rate. Another observation made in these studies was that a dose of prednisolone of 7.5 mg day^{-1} appeared to be the threshold dose for the development of osteoporosis.

Another approach to evaluating the risk of osteoporosis in patients treated with corticosteroids is to measure bone-mineral density. The technology has recently improved so that accurate and precise measurements may now be made of the bone susceptible to fracture (vertebrae and proximal femur). In postmenopausal women, a decrease of 1 standard deviation (or about 12%) in bone-mineral density is associated with a doubling of fracture risk at the site measured [7]. This relationship may be an underestimate in patients treated with corticosteroids as the 'fracture threshold' appears to be higher than in postmenopausal osteoporosis [8].

The most rapid rate of bone loss occurs in the 1st year of treatment [9, 10] and is similar for the lumbar spine and femoral neck. Similarly, in cross-sectional studies of patients treated with corticosteroids, there was a similar decrease in bone-mineral density of the lumbar spine and femoral neck. There is some disagreement whether the bone loss from the spine is both cortical and trabecular based on computed tomography and dual-energy X-ray absorptiometry (DXA) studies [11–13]; however, these differences in interpretation may be partly explained by the effect of corticosteroids on the proportion of the bone marrow that is fat. These studies report decreases of about 10–15% over age-matched controls, and this would be consistent with a doubling of the risk of fracture.

The use of corticosteroids is on the increase: over the past 3 years, there has been a 75% increase in prescriptions for corticosteroids used in respiratory disease in Hampshire, UK (Prescription Pricing Authority, 1993) (Fig. 1). Respiratory disease is the commonest indication for the prescription of corticosteroids (Peat *et al.*, unpublished observation) both in hospital and in general practice. In the general practice setting, there are 40 prescriptions of inhaled steroid for every prescription for orally administered corticosteroids. High-dose inhaled corticosteroids may have similar effects on bone density [14] and bone turnover (see below) as orally administered corticosteroids.

How do corticosteroids cause osteoporosis?

The mechanism of corticosteroid-induced osteoporosis appears to be different to that of postmenopausal osteoporosis. The major change in corticosteroid-induced osteoporosis is a decrease in osteoblast activity that results in a decreased work rate by osteoblasts (mean appositional rate) [15–18], and a decreased active life span of osteoblasts [19]. This differs from postmenopausal osteoporosis in which there is normal mineral appositional rate but a decreased active life span of osteoblasts and an increased activation frequency [20]. The decrease in bone formation has also been observed using biochemical markers of bone turnover, especially osteocalcin. Corticosteroids result in a dose-dependent decrease in osteocalcin within 4 days of starting treatment [21–25]. A dose of prednisolone of 20 mg day^{-1} may be associated with a 50% reduction in osteocalcin levels [26], similar to the effect of high-dose inhaled budesonide [27]. Osteocalcin may overestimate the effect of corticosteroids on collagen synthesis by osteoblasts [28]. However, a similar time-course (if not magnitude) of suppression was

observed using a marker of type I collagen synthesis – procollagen type I C-terminal propeptide [29]. The decrease in bone formation results in a decrease in the mean wall thickness [19, 30].

The cellular mechanisms of corticosteroids on bone have been identified in part [31]. Corticosteroids have direct effects on osteoblasts to decrease the production of cytokines and locally acting factors (PGE_2, TNF-α, IL1-β) and decrease the activity of IGF-1. They also decrease the production of these locally acting cytokines produced by monocytes in the marrow micro-environment. Vitamin D resistance may be a common feature of other forms of osteoporosis. Godschalk *et al.* [32] reported that corticosteroids decreased the number, but not the affinity, of calcitriol receptors in human osteosarcoma cell lines. The evidence that corticosteroids cause increased bone resorption is less convincing. This may be because there is no change in bone resorption or because the methods available for evaluating bone resorption have been less reliable than those for bone formation. Studies using radiotracer kinetics appeared to show increased bone resorption [33, 34]. Studies using bone histomorphometry have shown increased bone resorption surfaces [17], and a trend towards increased osteoclast number [17] and increased eroded surfaces [17, 35]. Again, these studies may be criticized in that the increased bone resorption may reflect the underlying disease. Urinary hydroxyproline has been used to study prospectively the effect of corticosteroids. Two studies showed an increase [27, 36], one showed no change [23] and two showed a decrease [16, 24]. These contradictory results may be due to an effect of corticosteroids on the underlying disease, or an effect of corticosteroids on the turnover of collagen from tissues other than bone – hydroxyproline reflects breakdown (and synthesis) of collagen from all sources. A more specific marker of bone resorption is deoxypyridinoline. This has not yet been used in a prospective study; in a cross-sectional study, corticosteroids appeared to have no effect on its excretion [14].

It has been proposed that these changes in bone turnover result from secondary hyperparathyroidism and that this, in turn, results from decreased intestinal calcium absorption and increased urinary excretion of calcium [37, 38]. Marcus [39] has challenged the central role of parathyroid hormone, claiming that the evidence is based on assays that measure hormone fragments [40–43], whereas assays that measure intact parathyroid hormone [9, 24] or even prospective studies measuring mid-region fragment [23, 44, 45] did not show any change in parathyroid hormone levels. The lack of effect on bone loss of corticosteroids given to animals after parathyroidectomy may result from increased bone sensitivity to parathyroid hormone after corticosteroid therapy.

Lukert & Raisz have concluded that there is a decrease in calcium absorption as a result of corticosteroid use and that absorption in the duodenum is most affected, and that this results from decreased synthesis of vitamin-D-binding protein [31]. This decrease was not a result of changes in the active form of vitamin D (calcitriol), as levels were normal and calcitriol therapy did not restore calcium absorption to normal. More recent studies in patients contradict these conclusions. Luengo *et al.* and Morris *et al.* reported normal calcium absorption in patients taking corticosteroids, except in those with fractures [46, 47]. Colette *et al.* reported similar increases in fractional calcium absorption in patients treated with corticosteroids to controls, although the peak absorption rate was slower than in controls [48]. There is some evidence that there is decreased tubular reabsorption of calcium [49] but this may only be present at high doses of prednisolone (25 mg day^{-1}) and the increase in urinary calcium may be explained by a greater filtered load resulting from an increase in serum calcium [24].

Other factors may play a role in the development of corticosteroid-induced osteoporosis. Sex steroids are important determinants of bone turnover. Corticosteroids therapy may result in a dose-dependent decrease in serum testosterone [38]. In postmenopausal women, the major source of androgens and oestrogens is the adrenal, and the adrenal suppression resulting from corticosteroid therapy results in decreased production of androstenedione, testosterone, and oestrone [50] and in the premenopausal woman there may be inhibition of FSH-stimulated oestrogen [51]. The resultant hypogonadism may result in increased bone turnover and bone loss.

In summary, there is a decrease in bone formation and perhaps an increase in bone resorption (and activation frequency) as a result of corticosteroid therapy. Thus, there are more bone-remodelling cycles and during each remodelling cycle there is an

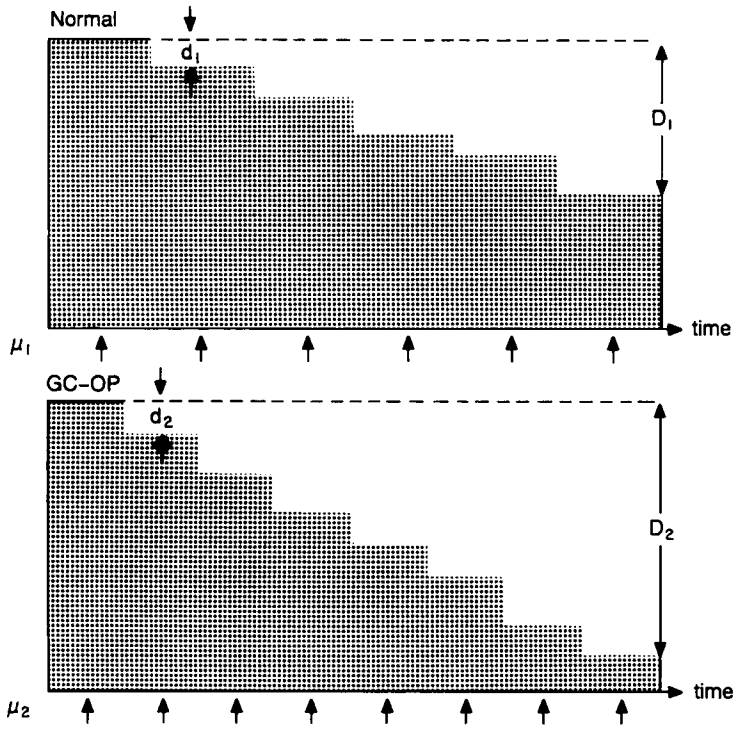

Fig. 2 Mechanism of bone loss in corticosteroid-induced osteoporosis, compared to normal ageing. The activation frequency (m) is increased, and the remodelling imbalance (d) is more marked in corticosteroid-induced osteoporosis, resulting in greater bone loss (D). From Dempster *et al.* [19], with permission.

imbalance between bone resorption and bone formation (remodelling imbalance) (Fig. 2). This differs from postmenopausal osteoporosis in which the increase in activation frequency dominates over the remodelling imbalance. As a result of the difference in mechanism, the trabecular bone architecture differs between the two conditions. Aaron *et al.* reported that in corticosteroid-induced osteoporosis there was thinning of trabeculae with a small reduction in trabecular number, whereas in idiopathic osteoporosis the trabeculae were of normal width, but were fewer, indicative of trabecular perforation [15]. The different mechanisms by which osteoporosis develops may also result in different responses to antiresorptive therapy. If this proposed model is correct, then antiresorptive drugs may be less effective in corticosteroid-induced osteoporosis, whereas formation-stimulating therapy would have a normal trabecular pattern on which to build new bone in corticosteroid-induced osteoporosis.

Therapy for corticosteroid-induced osteoporosis

Therapy for preventing further bone loss could be started:

1 At the onset of corticosteroid therapy (primary prevention);
2 after low bone density has developed, but fractures have not yet occurred (secondary prevention);
3 after fractures have occurred (treatment).

Various strategies could be taken to prevent bone loss. The agents listed here are currently available in the UK and may not be approved for use elsewhere.
1 Modification of lifestyle factors known to affect bone, e.g. limit cigarette and alcohol consumption, encourage weight-bearing activity.
2 Reduction in corticosteroid doses to below levels thought harmful to bone (aim for 5 mg day^{-1} or less).
3 Use of a corticosteroid that may have less effect on bone, e.g. deflazecort. This drug has not been approved for use in the UK yet. If the effective dose ratio to prednisolone is 6:5, then it may have less harmful effects on bone than prednisolone [52].
4 Alternative routes of administration (inhaled versus oral) may have less effect on bone but alternate day administration does not have less effect on bone.
5 Use of medications that inhibit bone resorption. The concern here is that if corticosteroids inhibit bone formation and a drug is given that inhibits bone resorption, then a state of very low bone turnover may result. Such a state may interfere with the repair of micro-fractures. Such a situation has not yet been

observed in man, although high-dose bisphosphonates have induced such a state in dogs.

6 Use of medications that stimulate bone formation. Sodium fluoride has been used in postmenopausal osteoporosis where it may result in an increase in bone-mineral density of 9% year^{-1} [53]. However, it results in little improvement in fracture risk because of the abnormal biomechanical properties of the newly formed bone. It is the one agent known to stimulate bone formation that has been evaluated in corticosteroid-induced osteoporosis. An increase in trunk calcium was observed in 22 subjects with miscellaneous conditions treated for 4 years. The increase in bone density may not result in a decrease in fracture risk [53] and so the results of such a study need to be interpreted with caution.

Bisphosphonates

Two bisphosphonates have been evaluated in this setting. Etidronate is usually given in a cyclical fashion to prevent mineralization defects developing. This regimen has been reported to decrease the incidence of vertebral fractures in patients with postmenopausal osteoporosis [54].

Pamidronate does not cause mineralization defects at the dose currently used, but it commonly causes gastrointestinal intolerance if given orally, and an acute-phase response (fever and leucopenia) if given intravenously.

Primary prevention

There has been only one study of primary prevention of bone loss using bisphosphonates. Mulder & Struys studied 20 patients with temporal arteritis treated with high-dose steroids and randomized them to receive cyclical etidronate or no therapy for 1 year. They found that the bone loss from the spine (measured by DXA) could be prevented by the bisphosphonate [55].

Secondary prevention

There have been three studies of the secondary prevention of bone loss using bisphosphonates, but only one of them had a randomized study design. Reid *et al.* studied 40 patients treated with prednisolone (12–15 mg day^{-1}) for about 5 years, who were randomized to receive pamidronate and calcium. After 1 year there was an increase of 20% in the bone density of the spine (by computed tomography), compared to a decrease of 9% in the placebo-treated group. The benefit persisted into the 2nd year and was associated with the expected decrease in bone turnover (assessed by urinary hydroxyproline and serum osteocalcin) [56, 57]. Gallagher *et al.* studied 17 patients with respiratory disease treated with prednisolone (mean, 14 mg day^{-1}) for about 14 years; all received intravenous pamidronate every 3 months for 1 year. There was a significant increase in bone-mineral density of the lumbar spine, but not of the hip, and the expected decrease in bone turnover (urinary hydroxyproline and total alkaline phosphatase activity) [58].

Adachi *et al.* studied 68 patients with miscellaneous diseases treated with prednisone (mean, 9 mg day^{-1}) for a mean duration of 6 years, and 35 were assigned to cyclical etidronate based on low bone mass or rapid rate of bone loss. There were 33 concurrent controls. Both groups received calcium supplement. There was a significant increase of 4% in the etidronate group, compared to a decrease of 2% over 1 year in the control group at the lumbar spine, but no change in the proximal femur (both measured by DXA) [59].

Hormone replacement therapy: secondary prevention

There has only been one study of the use of hormone replacement therapy in the secondary prevention of bone loss. Lukert *et al.* studied 15 patients with asthma treated with prednisone (mean, 8 mg day^{-1}) for a mean duration of 3 years. Eight subjects received conjugated equine oestrogens and medroxyprogesterone acetate for 1 year and seven subjects received no additional treatment. There was a significant increase in bone density at the lumbar spine in women treated with hormone replacement therapy, but not in the control group. The increase in bone density as a result of HRT was as great in women taking corticosteroids as those not taking corticosteroids [60].

Vitamin D

Primary prevention

There has been one study using calcitriol (the active form of vitamin D) in the primary prevention of corticosteroid-induced bone loss. Sambrook *et al.* [9] studied 103 patients with miscellaneous diseases within 4 weeks of the onset of treatment with prednisone, and the patients were randomized to 1 year's treatment with calcium with or without calcitriol or calcitriol plus intranasal calcitonin. They were followed up for a further year after stopping treatment. Sixty patients completed the 2-year study. The bone loss from the lumbar spine in the calcium-alone group was 4% $year^{-1}$ and this loss was prevented by calcitriol (with or without calcitonin). There was no protection against the bone loss at the distal radius or proximal femur. In the 2nd year there was continued bone loss from the spine in the calcium group and bone loss in the calcitriol group, but not from the spine in the group that had received calcitriol and calcitonin. This latter finding is difficult to explain in view of the short half-lives of both calcitonin and calcitriol. It may have resulted from them receiving less corticosteroids in the 2nd year than the calcitriol alone group. The use of calcitriol has the attraction that it has been shown in short-term studies to reverse the suppression of osteocalcin induced by corticosteroids [6, 25]. The drawback to its use is the high prevalence of hypercalcaemia (25%) at the dose of 0.5 to 1 mg day^{-1} used in this study.

Secondary prevention

The early studies using vitamin D in its various forms – 1α-hydroxyvitamin D [62] and dihydrotachysterol [63] – gave conflicting results.

Calcitonin

Primary prevention

There has been one primary prevention study of the use of calcitonin alone in the prevention of corticosteroid-induced bone loss. Montemurro *et al.* [64] studied 68 patients with sarcoidosis at the onset of treatment with prednisone and the patients were treated with calcitonin or nothing; the subjects were not randomized to the treatment groups, nor were the groups studied concurrently. The calcitonin was given intramuscularly for 24 months in 18 subjects and intramuscularly for 4 months and then intranasally for 20 months in 11 subjects. In the untreated group, there was bone loss at the spine (measured by computed tomography) of 15% over 2 years, and this bone loss was prevented in the two calcitonin-treated groups.

The only other report to appear in a peer-reviewed journal is by Sambrook *et al.* [9], which is discussed above.

Management of the individual patient

It is difficult to establish clear guidelines for the management of the individual patient as there are limited data on which to base these guidelines. The following represent approaches used by the physicians at the Consensus Group Meeting.

Primary and secondary prevention

In patients in whom it is probable that a course of corticosteroids will last for more than 6 months, consider measuring bone-mineral density of the lumbar spine and proximal femur by DXA.

1 In all patients, recommend the general measures (avoidance of smoking, sensible alcohol consumption, regular exercise, prevention of falls).

2 In patients with bone-mineral density 1 SD below the expected level for age (or 2.5 SD below the level found in young subjects), or if the mean dose is likely to be more than 15 mg day^{-1} prednisolone, then recommend hormone replacement therapy in postmenopausal women. If hormone replacement therapy is contraindicated then go to **3.** Repeat bone-mineral density measurement after 1 year and if the rate of loss from the lumbar spine is greater than 4% $year^{-1}$, go to **3**.

3 In patients with bone-mineral density 1 SD below the expected level for age (or 2.5 SD below the level found in young subjects), consider changing from prednisolone to deflazecort. Consider primary prevention of bone loss with a bisphosphonate such as cyclical etidronate, or consider calcitriol (but there is a need to monitor serum and urinary calcium). In men, measure testosterone and replace if necessary.

Treatment

In patients who develop fractures whilst taking corticosteroids, the usual practice is the same as for patients with idiopathic osteoporosis.

1 Ensure that fracture is present e.g. lateral radiograph of thoracic and lumbar spine.

2 Ensure that there is no other contributory cause for the osteoporosis by measuring full blood count, erythrocytes sedimentation rate, serum TSH, protein electrophoresis, serum calcium, phosphate, alkaline phosphatase, creatinine, 24-h urinary calcium and creatinine, and (in men) serum testosterone.

3 Evaluate degree of bone loss by DXA to give prediction of prognosis and for monitoring therapy.

4 Treat with hormone replacement therapy or a bisphosphonate (such as cyclical etidronate or pamidronate) for the duration of the corticosteroid treatment.

5 If these treatments are ineffective or unsuitable, then consider calcitriol or calcitonin. Other treatments such as anabolic steroids, ipriflavone and fluoride have been studied less than the above treatments.

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Correspondence: Dr Richard Eastell, Department of Human Metabolism and Clinical Biochemistry, Clinical Sciences Centre, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK.