

REVIEW

Glucocorticoid osteoporosis – mechanisms and management

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Abstract

Glucocorticoids are potent osteopenic agents, producing negative calcium and bone balance via actions at many sites. The most significant adverse effects of glucocorticoid drugs on the skeleton are probably a direct inhibition of matrix synthesis by the osteoblast, reductions in calcium absorption in both the gut and the renal tubule, and the production of hypogonadism, particularly in men. Reductions in bone density of 10–40% result, the loss being more marked in trabecular bone and in patients receiving a high cumulative dose of the steroid. Fractures occur in about 30% of individuals who take these drugs for an average of 5 years. Bone loss is reversible when glucocorticoid treatment is withdrawn. Bone density can also be increased by sex hormone replacement in those with demonstrable deficiency, by bisphosphonates, and possibly by vitamin D metabolites. All patients treated with glucocorticoids for more than 6 months should be considered for bone densitometry and be offered appropriate drug treatment if values are towards the lower end of the young normal range or if there is already evidence of fractures occurring after minimal trauma. With this approach, the significant morbidity associated with steroid osteoporosis might be substantially avoided.

European Journal of Endocrinology 137 209–217

Introduction

The first clinical descriptions of glucocorticoid excess were provided by Harvey Cushing nearly 70 years ago and included the development of symptomatic osteoporosis. In the 1940s and 1950s, glucocorticoid drugs were introduced into clinical practice, providing a lifesaving treatment for a diverse group of conditions including asthma, rheumatoid arthritis and many other inflammatory diseases. However, within a few years of their introduction, reports appeared of fractures occurring after minimal trauma in patients receiving steroids, and glucocorticoid-induced osteoporosis has remained a clinical problem. Since that time, however, our understanding of the mechanisms of glucocorticoid effects on bone have increased considerably, bone densitometry has become a widely available clinical tool allowing an estimation of fracture risk in steroid-treated patients, and a number of treatments have been demonstrated to increase bone mass in these patients. These advances should make it possible for patients to reap the therapeutic benefits of glucocorticoids whilst minimising the likelihood of suffering a fracture as a consequence.

Actions of glucocorticoids on bone and calcium metabolism

Glucocorticoids affect bone in many ways. They adversely affect bone formation, bone resorption, calcium entry

into the body in the gut and calcium exit from the body in the renal tubule. Thus the challenge has not been to find mechanisms by which glucocorticoids influence bone mass, but to determine which is the most important and, thus, the preferred target for any treatment aimed at averting steroid osteoporosis.

Osteoblasts

The osteoblast is one of the bone cells principally affected by glucocorticoids. Many of the effects are directly mediated through the osteoblast's glucocorticoid receptor, resulting in increased differentiation of osteoblast precursor cells but reduced proliferation and matrix synthesis in mature osteoblasts. In particular, the mRNAs for type I collagen (1) and the principal non-collagenous protein of bone, osteocalcin (2), are reduced by glucocorticoids, which also modulate mRNAs for osteopontin, fibronectin, β_1 -integrin, bone sialoprotein and the insulin-like growth factors (3). The activity of the last of these factors is modulated by the concentrations of both stimulatory and inhibitory binding proteins, which are themselves influenced by glucocorticoids in a way that reduces the growth-stimulatory activity of these factors (4, 5).

These changes in the activity of individual osteoblasts are reflected in changes in bone histomorphometry which, in both animal and human studies, consistently demonstrates that glucocorticoid treatment is associated

with reduced rates of bone formation and reduced periods of bone formation within each remodelling cycle (6). This reduction in bone formation is detectable clinically by reduced circulating concentrations of osteocalcin (7) and the C-terminal pro-peptide of type I pro-collagen (8), both markers of osteoblast activity.

Osteoclasts

In contrast to the consistent finding of reduced osteoblast activity, the effects of glucocorticoids on bone resorption are less clear. *In vitro* studies in isolated osteoclasts and bone organ cultures show either stimulation or inhibition of bone resorption, depending upon the precise experimental conditions. A number of histomorphometric studies in humans have suggested that static parameters of bone resorption are increased (6, 9) though Aaron *et al.* (9) reported that most of the resorptive surface was inactive and might simply reflect the slowness of refilling of resorption lacunae in the presence of glucocorticoids. Others have not confirmed this observation (10, 11). In general, studies measuring concentrations of the commonly used biochemical markers of bone resorption have not shown these to be increased in steroid-treated patients (8, 12) though, again, contrary results have been reported (12, 13). The balance of data suggests that the changes in resorption are less marked than those in formation and this is consistent with the histological picture seen in steroid-treated patients, in whom the trabeculae are thinned rather than perforated.

Intestinal absorption of calcium

Malabsorption of calcium is a fairly consistent (but not universal) finding in steroid-treated patients (14, 15). It is demonstrable within the first 2 weeks of steroid treatment, at which time concentrations of vitamin D metabolites are either normal or increased (16), suggesting that it is not mediated by changes in vitamin D metabolism. A reduction in concentrations of the vitamin D-dependent calcium-binding protein that is involved in intestinal calcium transport may contribute to this calcium malabsorption (17).

Urinary excretion of calcium

Sustained glucocorticoid excess results in marked hypercalciuria, and fasting urine calcium excretion is double control values in steroid-treated patients (18). Again, this has been a consistent finding in a number of different studies (12) and is probably mediated by a direct effect on renal tubular calcium reabsorption.

Vitamin D

There is little evidence to support the contention that changes in vitamin D metabolism contribute significantly

to the development of steroid osteoporosis. Prospective studies of patients or normal individuals beginning steroid treatment have shown no changes in 25-hydroxyvitamin D or 24,25-dihydroxyvitamin D, but significant increases in 1,25-dihydroxyvitamin D have been observed 2–15 days after initiation of treatment (12). There is no evidence for glucocorticoid effects on concentrations of vitamin D binding protein (19).

Parathyroid hormone

Many studies have assessed circulating concentrations of parathyroid hormone both longitudinally and cross-sectionally, in steroid-treated patients. Some, but not all (12, 20), have found evidence of hyperparathyroidism. This is consistent with evidence that glucocorticoids increase release of parathyroid hormone from cultured parathyroid tissue (21, 22). There is also evidence that osteoblast sensitivity to parathyroid hormone may be increased in the presence of glucocorticoids (23).

Phosphate metabolism

Cosman *et al.* (12) have demonstrated a transient reduction in renal tubular reabsorption of phosphate after large intravenous doses of methylprednisolone. This occurred before any changes in parathyroid hormone concentrations were detectable, and suggests that glucocorticoids may have a direct effect on the renal handling of this mineral. They may also directly inhibit gastrointestinal absorption of phosphate (24).

Sex hormones

Some of the changes in bone and calcium metabolism in glucocorticoid-treated patients may be contributed to by changes in concentrations of sex hormones. Men receiving glucocorticoid drugs have a dose-related reduction in circulating testosterone concentrations of nearly 50% in comparison with controls (25, 26). This probably results from inhibition of gonadotropin secretion and reduction in numbers of gonadotropin-binding sites in the testis. High-dose steroid therapy is associated with oligomenorrhoea in women, suggesting an effect on the pituitary–gonadal axis similar to that seen in men. Glucocorticoids markedly reduce adrenal androgen production in both sexes.

Bone density in glucocorticoid-treated patients

Exposure to supraphysiological doses of glucocorticoids leads to a substantial and rapid loss of bone. The limited prospective data available suggest that bone loss takes place in virtually all individuals (27, 28). Bone loss is most marked in the first 12 months (29), but continues long term, albeit at a lower rate (30). A prospective study has shown an 8% decrement in the trabecular

bone of the lumbar spine after 20 weeks of treatment with prednisone in a mean dose of 7.5 mg/day (28). Cross-sectional studies in patients treated for periods of 5 years show that integral bone mass of the lumbar spine and proximal femur is 20% below control values (31). Bone loss occurs more rapidly in trabecular than in cortical bone and decrements approaching 40% are seen in cross-sectional studies of the trabecular bone of the lumbar spine, whether assessed by quantitative CT scanning (32) or by dual energy x-ray absorptiometry in the lateral projection (33). Concern has been expressed that some of this apparent bone loss is artefactual, arising from the altered distribution of fat, particularly marrow fat, in the presence of steroid excess. There is little evidence that marrow fat is changed in Cushing's syndrome (34), and the bone loss observed in studies using either dual energy CT scanning (28) or bone biopsies (29) is similar to that found with single energy CT and dual energy x-ray absorptiometry, implying that soft-tissue changes do not have a significant influence on the changes found with the latter techniques.

In cross-sectional studies, the distribution of bone density is unimodal with a standard deviation comparable to that of the normal population. This implies that there is little between-patient variability in the extent of steroid-induced bone loss. Because the degree of bone loss is usually less than the range of values in the normal population, those patients whose bone densities before treatment were at the upper end of the normal range still have 'normal' bone densities. The degree of steroid-induced bone loss is related to average steroid dose and to the duration of treatment (32, 35, 36).

The bone loss induced by glucocorticoids is substantially reversible after the withdrawal of these drugs. Two prospective studies have demonstrated a reaccumulation of bone density over approximately the same time span as its loss occurred (27, 28). Substantial increases in bone density have been reported after cure of Cushing's syndrome (37, 38) and we have demonstrated that bone density is normal in patients cured of Cushing's syndrome for a mean period of 9 years (39). Alternate-day administration of the glucocorticoids, however, does not diminish bone loss (40–42).

For a number of steroid-responsive conditions, it is now possible to administer these drugs locally, thereby reducing systemic side effects. However, there is usually some systemic absorption of locally administered steroids, whether they are given by inhalation, as an enema, or by direct application to the skin. Inhalation of beclomethasone or budesonide in daily doses of less than 1 mg does not appear to influence bone metabolism in adults, but it has been reported recently that beclomethasone 400 µg/day produces significant growth retardation in children (43). While it is true that locally administered steroids will have a lesser osteopenic effect for a given concentration of therapeutic efficacy, these routes are certainly not completely free of skeletal side effects.

Incidence of fracture in glucocorticoid-treated patients

The osteopenia produced by glucocorticoids is associated with an increased risk of fracture, fracture prevalence averaging about 30% in adults treated for 5 years or longer. Because the most marked effects of glucocorticoids are on trabecular bone mass, it is, in particular, fractures at trabecular sites such as the vertebrae and ribs that are most common; however, hip fractures are also significantly increased (44). Longer periods of steroid use, age, sex and body weight all influence fracture risk (45). In non-steroid-treated patients, a previous history of low trauma fracture is a major risk factor for future fracture, irrespective of bone density. This is also likely to be the case in steroid-treated patients, as previous fracture provides evidence that the skeleton has reached a point at which it is not able to withstand the stresses routinely placed upon it. Therefore, patients with previous fractures should usually be offered prophylaxis against further bone loss, whatever their bone density.

Fracture prevention

General measures

The main thrust in preventing fractures in steroid-treated patients is to optimise their bone density; however, consideration of other factors such as falls prevention is also important. The dose-dependency and reversibility of steroid-induced osteoporosis suggest that minimisation of dosage or withdrawal of steroids are important in the management of these patients. The reduction in the effective systemic dose of glucocorticoids as a result of their topical administration is an important avenue to explore. Alternate-day steroid administration appears to be effective in reducing growth retardation in children, but it does not seem to diminish the osteopenic effects of glucocorticoids (40, 41). Lifestyle modifications intended to increase bone mass are also important. Thus patients should be encouraged not to smoke, to minimise alcohol intake, to maintain their body weight and to remain physically active.

Calcium

The deleterious effects of glucocorticoids on calcium transport in both the gut and renal tubule suggest that the administration of high doses of oral calcium might significantly improve bone mass. Unfortunately, there is little experimental evidence to support this contention. Nilsen *et al.* (46) demonstrated a slight reduction in the rate of radial bone loss in patients with rheumatoid arthritis who were given 6 g/day hydroxyapatite. Reid and Ibbertson (47) demonstrated significant suppression of bone resorption (measured as hydroxyproline

excretion) with 1 g/day elemental calcium supplementation. However, in a number of prospective studies in which calcium supplements of this magnitude were administered to the control groups, it has been shown that calcium alone will not prevent steroid-induced bone loss (48–50). This implies that steroid osteoporosis is not merely a problem with mineral balance, but is primarily related to reduced bone matrix synthesis, comparable to the wasting that occurs in soft tissues such as skin and muscle. Thus the therapeutic task is not merely to provide more substrate for bone synthesis, but also to reverse the catabolic effects of glucocorticoids on the skeleton.

Sex hormones

Oestrogen and testosterone are believed not to interfere specifically with the actions of glucocorticoids. Thus their use is not advocated as glucocorticoid antagonists, but rather as treatment for any co-existing sex hormone deficiency, with a view to correcting this additional risk factor for bone loss. In premenopausal women menstruating regularly, sex hormone replacement does not have a place. In postmenopausal women receiving steroids, the increases in bone density after the institution of conventional hormone replacement therapy are at least as great as those that occur in other postmenopausal women (51–55). There is also some evidence that sex hormone replacement improves control of rheumatoid arthritis (54, 56), one of the conditions for which glucocorticoids are commonly prescribed.

In steroid-treated men, circulating testosterone concentrations are reduced by almost 50% – a factor likely to contribute to the development of osteopenia. We have recently shown that testosterone replacement produced a 5% increase in lumbar spine bone mineral density after 12 months, in addition to reversing the accumulation of body fat and loss of lean tissue that accompany steroid treatment (57). Androgens, in the form of anabolic steroids, have also been used for treating steroid-induced osteoporosis. They would seem to have little place in the management of men, in whom they are likely to reduce testosterone concentrations further. Their use in women is associated with beneficial effects on bone mass, but also with virilising side effects in almost 50% of treated patients (58, 59).

A novel use of sex hormones in the treatment of steroid osteoporosis has been proposed by Greco *et al.* (60), who utilised the ability of progesterone to block the binding of glucocorticoids to their receptor. They showed that bone mass increased in steroid-treated men given medroxyprogesterone acetate. However, the use of such a non-specific glucocorticoid antagonist would be expected to interfere with the therapeutic action of the glucocorticoid, thus defeating the purpose of giving the treatment in the first place. Continuous progestogen treatment should not be given to premenopausal women

with steroid osteoporosis, as it results in oestrogen deficiency and bone loss (61).

Bisphosphonates

Bisphosphonates provide an attractive treatment for steroid osteoporosis, offering the potential to redress directly the imbalance between bone formation and resorption. They can be used in virtually all steroid-treated patients including the young and sex-hormone-replete. The bisphosphonate nucleus consists of two phosphate groups joined through a central carbon atom, the individual members of the group differing only in the side groups attached to that carbon atom. The clinically relevant difference between individual bisphosphonates is their antiresorptive potency, though most of the newer agents appear to achieve a comparable maximal inhibition of bone resorption.

The bisphosphonates are now becoming widely used in the management of postmenopausal osteoporosis, but their efficacy was first demonstrated in a randomised controlled trial of the treatment of steroid osteoporosis (48, 49). This trial showed that there was a 19% increase in the density of the trabecular bone of the lumbar spine after 12 months of treatment with pamidronate, compared with a 9% decrease in those receiving placebo. There were smaller but statistically significant benefits in the cortical bone mass of the metacarpals. In those patients proceeding to a second year of treatment, the gains in bone density were maintained, whereas there was progressive loss in the placebo group. Oral pamidronate is not widely available, but three-monthly infusions of 30 mg of this drug appear to be comparably effective (62).

There is now a number of studies showing that cyclic etidronate is effective in steroid-treated patients (63–65), and this treatment has high patient acceptability, as medication is taken for only 2 weeks every 3 months. The other widely available oral bisphosphonate, alendronate, is now well established as an effective treatment for postmenopausal osteoporosis. While the results of trials with this agent in steroid osteoporosis are still awaited, it would seem highly likely that alendronate in a daily dose of 10 mg will produce effects comparable to those seen with etidronate or pamidronate.

All bisphosphonates are very insoluble and therefore have a low oral bioavailability. To derive benefit from oral dosing, the patient must take them fasting with water at least 30 min before food, at a time separated by some hours from the ingestion of mineral supplements (such as calcium or iron) or antacids. Rarely, these drugs cause gastrointestinal irritation, including oesophageal erosions in those with gastro-oesophageal reflux.

Vitamin D and its metabolites

This group of compounds has been evaluated as treatment for steroid osteoporosis over several decades, but

the inconsistencies in the outcomes of the various studies mean that their place remains uncertain. Much of the early work in humans was carried out by Hahn and co-workers. They demonstrated significant increases in forearm bone density from the use of calciferol 50 000 U three times per week plus calcium 500 mg/day (66). In a subsequent study using 25-hydroxyvitamin D (40 µg/day), similar beneficial effects on bone density were found (67). The group then investigated the role of calcitriol (0.4 µg/day) and again found increases in forearm density, but these were no different from the increases found in the control group given calcium alone (68). Subsequently Braun *et al.* (10) demonstrated a beneficial effect of alphacalcidol (2 µg/day) on trabecular bone volume over a 6-month period; however, Bijlsma *et al.* (69) in a 2-year study, failed to show any benefit from the use of dihydrotachysterol. In 1989, Di Munno *et al.* (70) reported a substantial gain in radial bone mineral content in patients starting to receive glucocorticoids who were also given 25-hydroxyvitamin D (35 µg/day), compared with substantial losses in those given placebo.

Sambrook *et al.* (50) reported a large study in which patients beginning glucocorticoid treatment were randomly assigned to receive calcium, calcium plus calcitriol (mean dose 0.6 µg/day) or these two agents combined with calcitonin over a 12-month period. Bone loss from the lumbar spine was 4.3%, 1.3% and 0.2% in the respective groups. There was a similar, non-significant trend in distal radial bone loss, but no evidence whatsoever of reduced bone loss in the proximal femur (3% in all groups). While there was clearly a benefit from the use of calcitriol, it was less than that seen in a comparable trial in which etidronate was administered from the time of introduction of steroid treatment (71); several other groups have also documented that etidronate prevents femoral bone loss (64, 65). In contrast, when the effects of alphacalcidol and etidronate were compared in a recent study of bone loss after cardiac transplantation (72), neither treatment completely prevented bone loss, though the vitamin D metabolite was superior to the bisphosphonate. It should be noted, however, that many of the patients in that study were vitamin D deficient. Adachi *et al.* (73) have recently re-examined the effect of calciferol (50 000 U/week) plus calcium (1000 mg/day) in a randomised controlled trial. At the end of 3 years, they found no suggestion of any beneficial effect from the use of this intervention. This contrasts with the findings of Buckley *et al.* (74), who showed prevention of bone loss with calcium (1000 mg/day) and calciferol (500 U/day) in their patients, most of whom were already established on steroid treatment. It is unclear whether the different outcomes of these studies relate to the dose of vitamin D used, the initial vitamin D status of the patients, or different effects of these interventions in patients initiating or continuing steroid treatment.

The relatively small number of studies with each agent and the variability of their outcomes make it difficult to determine the optimal course with respect to vitamin D and its metabolites in the prevention of steroid osteoporosis. The present author tends to use them as adjuncts to either sex hormone replacement or bisphosphonates in patients with severe steroid osteoporosis, or as second-line treatment in those for whom these other agents are not acceptable. Calciferol is always indicated to treat proven vitamin D deficiency (i.e. subnormal circulating concentrations of 25-hydroxyvitamin D).

Fluoride

Fluoride ion is a potent osteoblast mitogen that is capable of producing sustained gains in lumbar spine bone density with long-term treatment. This unique beneficial effect is counter-balanced by its interference with the normal mineralisation of bone when present in bone crystal at high concentrations. These opposing effects have made it difficult to translate the beneficial effects of fluoride on bone mass into reduced fracture incidence in postmenopausal osteoporosis. Work is continuing in that condition, to define the therapeutic window for its effective use. It is, in theory, an attractive agent for use in steroid osteoporosis because its greatest effects are on trabecular bone, the site of greatest bone loss in steroid-treated patients. There is now clear evidence that it can increase spinal bone density (75–77) and increase trabecular bone volume of the iliac crest (78) in steroid-treated patients. However, its antifracture efficacy in this context remains to be established, and it should not be used as a first-line agent in steroid osteoporosis. Its cautious use may be appropriate as an adjunctive treatment in patients with severe bone loss. Some authorities regard low proximal femoral bone density as a contraindication to the use of fluoride, as some studies have suggested that it can cause bone loss at this site.

Calcitonin

Calcitonin acts via specific receptors on osteoclasts, reducing bone resorption. It has been used in some countries for the management of postmenopausal osteoporosis, though its effectiveness is generally less than that of hormone replacement therapy or the bisphosphonates. There have now been several controlled trials in steroid-treated patients that suggest that it slows bone loss. Thus Rizzato *et al.* (79) found that injections of salmon calcitonin (100 IU every 1–2 days) prevented bone loss over a 15-month period, whereas vertebral bone mass declined 14% in the control group. Using a similar regimen, Luengo *et al.* (80) found an increase in spinal bone density of 4% in those receiving calcitonin, whereas this index decreased by 2.5% in the control group over a 12-month period. Similar results

using intranasal calcitonin have been reported by Montemurro *et al.* (81). Thus calcitonin is likely to be effective, but its side effects and cost make it less attractive than sex hormone therapy or the bisphosphonates.

Thiazides

Thiazide diuretics have been advocated as a treatment for both postmenopausal and steroid-induced osteoporosis. They clearly diminish urinary calcium loss in steroid-treated patients (82, 83) and Yamada (84) has demonstrated that the addition of a thiazide to alphacalcidol and calcium leads to significantly more positive changes in bone mass in steroid-treated patients. However, there are no other studies demonstrating a beneficial effect on bone density and it is the present author's experience that hypokalaemia is rather more frequent in steroid-treated patients taking thiazides than in others.

Bone-sparing glucocorticoids

Deflazacort is a derivative of prednisone that has been suggested to exert lesser deleterious effects on calcium and bone metabolism than prednisone itself. Thus studies have demonstrated less marked hypercalciuria (85, 86), lesser effects on intestinal calcium absorption (85), reduced bone loss (87–90) and less growth retardation in children treated with deflazacort (91, 92). However, all these studies assumed that the potency of prednisone relative to deflazacort was 1.2. Subsequent re-examination of the relative potencies of these two glucocorticoids has found that the true relative potency is 1.4–1.8 (93, 94). Thus much of the earlier literature may be invalid because it has compared non-equivalent doses of the two agents. A recent study of bone density changes in patients with polymyalgia rheumatica in whom steroid doses were adjusted to produce symptom control also suggested that the glucocorticoid potency of deflazacort has been overestimated in the past, and demonstrated no bone-sparing effect of this agent when used in a therapeutically equivalent dose (95).

Who to treat

Many patients receiving steroid treatment do not develop fractures, whereas others will suffer a fracture within a few months of beginning these drugs. As outlined above, there is a wide range of potential treatments so the clinician requires strategies for selecting the appropriate intervention, if any, for each patient. The patients who should be treated with drugs that increase bone mass are those at highest risk of fracture. A past history of fractures after minimal trauma is clearly an indication for treatment. The other clinical risk factors for low bone mass are listed above

but, if possible, it is desirable that bone density should be measured directly. A bone density below the young adult normal range (i.e. more than 2–2.5 standard deviations below the young normal mean) indicates that that patient's immediate risk of fracture is significantly increased: each standard deviation change in bone density is associated with a twofold change in fracture risk. Patients whose bone density is in the lower one-third of the normal range may not be at immediate risk of fracture, but will become so if they continue treatment in the long term, or if there are other risk factors present (such as high glucocorticoid dose or concurrent sex hormone deficiency). Thus all these individuals should be considered for some bone-protective treatment.

Attention to lifestyle factors and the optimisation of calcium intake are sensible first-line measures, but are unlikely to reduce fracture risk substantially on their own. In patients at significant risk, these measures should be accompanied by a single drug intervention, usually either sex hormone replacement (if appropriate) or the use of a bisphosphonate. In an individual at very high fracture risk (multiple previous fractures, bone density more than 3.5 standard deviations below the young normal mean value) combinations of treatments are appropriate. Most of the available therapies can be used together. Hormone replacement therapy and bisphosphonates probably have additive effects, and a vitamin D metabolite (such as alphacalcidol or calcitriol) could be added to these. In the patient who continues to fracture or lose bone mass in spite of these measures, the cautious use of fluoride as an additional intervention may be appropriate. Low doses should be used (e.g. 15–20 mg fluoride ion/day) and it may be safer in a slow-release formulation. Giving fluoride simultaneously with calcium supplements slows its absorption and probably increases its safety.

The consideration of the possibility of steroid osteoporosis *before* it becomes clinically apparent, and the judicious use of the available interventions can greatly reduce the morbidity from this condition, increasing the safety and acceptability of these lifesaving medications.

References

- 1 Lukert B, Mador A, Raisz LG & Kream BE. The role of DNA synthesis in the responses of fetal rat calvariae to cortisol. *Journal of Bone and Mineral Research* 1991 **6** 453–460.
- 2 Morrison NA, Shine J & Fragonas J-C. 1,25-dihydroxyvitamin D-responsive element and glucocorticoid repression in the osteocalcin gene. *Science* 1989 **146** 1158–1161.
- 3 Chen TL, Mallory JB & Hintz RL. Dexamethasone and 1,25(OH)₂ vitamin D3 modulate the synthesis of insulin-like growth factor-I in osteoblast-like cells. *Calcified Tissue International* 1991 **48** 278–282.
- 4 Chevalley T, Strong DD, Mohan S, Baylink DJ & Linkhart TA. Evidence for a role for insulin-like growth factor binding proteins in glucocorticoid inhibition of normal human osteoblast-like cell proliferation. *European Journal of Endocrinology* 1996 **134** 591–601.
- 5 Gabbitas B & Canalis E. Cortisol enhances the transcription of

- insulin-like growth factor-binding protein-6 in cultured osteoblasts. *Endocrinology* 1996 **137** 1687–1692.
- 6 Dempster DW. Bone histomorphometry in glucocorticoid-induced osteoporosis. *Journal of Bone and Mineral Research* 1989 **4** 137–141.
 - 7 Reid IR, Chapman GE, Fraser TRC, Davies AD, Surus AS, Meyer J *et al.* Low serum osteocalcin levels in glucocorticoid-treated asthmatics. *Journal of Clinical Endocrinology and Metabolism* 1986 **62** 379–383.
 - 8 Lems WF, Gerrits MI, Jacobs JWG, Vanvugt RM, Vanrijn HJM & Bijlsma JWJ. Changes in (markers of) bone metabolism during high dose corticosteroid pulse treatment in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases* 1996 **55** 288–293.
 - 9 Aaron JE, Francis RM, Peacock M & Makins NB. Contrasting microanatomy of idiopathic and corticosteroid-induced osteoporosis. *Clinical Orthopedics* 1989 **243** 294–305.
 - 10 Braun JJ, Birkenhager-Frenkel DH, Rietveld Jr AH, Visser JTT & Birkenhager JC. Influence of $1\alpha(\text{OH})\text{D}_3$ administration on bone and bone mineral metabolism in patients on chronic glucocorticoid treatment: a double-blind controlled study. *Clinical Endocrinology* 1983 **18** 265–273.
 - 11 Hahn TJ, Halstead LR, Teitelbaum SL & Hahn BH. Altered mineral metabolism in glucocorticoid-induced osteopenia. *Journal of Clinical Investigation* 1979 **64** 655–665.
 - 12 Cosman F, Nieves J, Herbert J, Shen V & Lindsay R. High-dose glucocorticoids in multiple sclerosis patients exert direct effects on the kidney and skeleton. *Journal of Bone and Mineral Research* 1994 **9** 1097–1105.
 - 13 Gennari C, Imbimbo B & Montagnani M. Effects of prednisone and deflazacort on mineral metabolism and parathyroid hormone activity in humans. *Calcified Tissue International* 1984 **36** 245–252.
 - 14 Nordin BEC, Marshal DH, Francis RM & Crilly RG. The effects of sex steroid and corticosteroid hormones on bone. *Journal of Steroid Biochemistry* 1981 **15** 171–174.
 - 15 Klein RG, Arnaud SB & Gallagher JC. Intestinal calcium absorption in exogenous hypercortisonism. *Journal of Clinical Investigation* 1977 **60** 253–259.
 - 16 Hahn TJ, Halstead LR & Baran DT. Effects of short term glucocorticoid administration on intestinal calcium absorption and circulating vitamin D metabolite concentrations in man. *Journal of Clinical Endocrinology and Metabolism* 1981 **52** 111–115.
 - 17 Tohmon M, Fukase M, Kishihara M, Kadowaki S & Fujita T. Effect of glucocorticoid administration on intestinal, renal and cerebellar calbindin-D28K in chicks. *Journal of Bone and Mineral Research* 1988 **3** 325–331.
 - 18 Reid IR & Ibbertson HK. Evidence for decreased tubular reabsorption of calcium in glucocorticoid-treated asthmatics. *Hormone Research* 1987 **27** 200–204.
 - 19 Braun JJ, Juttman JR, Visser TJ & Birkenhager JC. Short-term effect of prednisone on serum 1,25-hydroxy-vitamin D in normal individuals and in hyper- and hypoparathyroidism. *Clinical Endocrinology* 1982 **17** 21–28.
 - 20 Fucik RF, Kukreja SC, Hargis GK, Bowse EM, Henderson WJ & Williams GA. Effect of glucocorticoids on function of the parathyroid glands in man. *Journal of Clinical Endocrinology and Metabolism* 1975 **40** 152–185.
 - 21 Au WYW. Cortisol stimulation of parathyroid hormone secretion by rat parathyroid glands in organ culture. *Science* 1976 **193** 1015–1017.
 - 22 Butler RC, Davie MWJ, Worsfold M & Sharp CA. Bone mineral content in patients with rheumatoid arthritis: relationship to low-dose steroid therapy. *British Journal of Rheumatology* 1991 **30** 86–90.
 - 23 Chen TL & Feldman D. Glucocorticoid receptors and actions in subpopulations of cultured rat bone cells. *Journal of Clinical Investigation* 1979 **63** 750–758.
 - 24 Gennari C, Bernini M & Nardi P. Glucocorticoids: radiocalcium and radiophosphate absorption in man. In *Osteoporosis, a Multidisciplinary Problem*. Eds ASJ Dixon, RGG Russell & TCB Stamp. London: Royal Society of Medicine, 1983.
 - 25 Reid IR, France JT, Pybus J & Ibbertson HK. Low plasma testosterone levels in glucocorticoid-treated male asthmatics. *British Medical Journal* 1985 **291** 574.
 - 26 Reid IR, Veale AG & France JT. Glucocorticoid osteoporosis. *Journal of Asthma* 1994 **31** 7–18.
 - 27 Rizzato G & Montemurro L. Reversibility of exogenous corticosteroid-induced bone loss. *European Respiratory Journal* 1993 **6** 116–119.
 - 28 Laan RFJM, Vanriel PLCM, Vandeputte LBA, Vanerning LJTO, Vanthof MA & Lemmens JAM. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis – a randomized, controlled study. *Annals of Internal Medicine* 1993 **119** 963–968.
 - 29 Lo Cascio V, Bonucci E, Imbimbo B, Ballanti P, Adami S, Milani S *et al.* Bone loss in response to long-term glucocorticoid therapy. *Bone and Mineral* 1990 **8** 39–51.
 - 30 Saito JK, Davis JW, Wasnich RD & Ross PD. Users of low-dose glucocorticoids have increased bone loss rates: a longitudinal study. *Calcified Tissue International* 1995 **57** 115–119.
 - 31 Reid IR, Evans MC, Wattie DJ, Ames R & Cundy TF. Bone mineral density of the proximal femur and lumbar spine in glucocorticoid-treated asthmatic patients. *Osteoporosis International* 1992 **2** 103–105.
 - 32 Reid IR & Heap SW. Determinants of vertebral mineral density in patients receiving chronic glucocorticoid therapy. *Archives of Internal Medicine* 1990 **150** 2545–2548.
 - 33 Reid IR, Evans MC & Stapleton J. Lateral spine densitometry is a more sensitive indicator of glucocorticoid-induced bone loss. *Journal of Bone and Mineral Research* 1992 **7** 1221–1225.
 - 34 Mayo-Smith W, Rosenthal DI, Goodsitt MM & Klubanski A. Intravertebral fat measurement with quantitative CT in patients with Cushing disease and anorexia nervosa. *Radiology* 1989 **170** 835–838.
 - 35 Hall GM, Spector TD, Griffin AJ, Jawad ASM, Hall ML & Doyle DV. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. *Arthritis and Rheumatism* 1993 **36** 1510–1516.
 - 36 Mateo L, Nolla JM, Rozadilla A, Rodriguezmoreno J, Niubo R, Valverde J & Roigescofet D. Bone mineral density in patients with temporal arthritis and polymyalgia rheumatica. *Journal of Rheumatology* 1993 **20** 1369–1373.
 - 37 Lufkin EG, Wahner HW & Bergstralh EJ. Reversibility of steroid-induced osteoporosis. *American Journal of Medicine* 1988 **85** 887–888.
 - 38 Hermus AR, Smals AG, Swinkels LM, Huysmans DA, Pieters GF, Sweep CF, Corstens FH & Kloppenborg PW. Bone mineral density and bone turnover before and after surgical cure of Cushing's syndrome. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 2859–2865.
 - 39 Manning PJ, Evans MC & Reid IR. Normal bone mineral density following cure of Cushing's syndrome. *Clinical Endocrinology* 1992 **36** 229–234.
 - 40 Chesney RW, Mazess RB, Rose P & Jax DK. Effect of prednisone on growth and bone mineral content in childhood glomerular disease. *American Journal of Diseases in Childhood* 1978 **132** 768–772.
 - 41 Gluck OS, Murphy WA, Hahn TJ & Hahn B. Bone loss in adults receiving alternate-day glucocorticoid therapy. *Arthritis and Rheumatism* 1981 **24** 892–898.
 - 42 Ruegsegger P, Medici TC & Anliker M. Corticosteroid-induced bone loss. A longitudinal study of alternate-day therapy in patients with bronchial asthma using quantitative computed tomography. *European Journal of Clinical Pharmacology* 1983 **25** 615–620.
 - 43 Doull I, Freezer N & Holgate S. Osteocalcin, growth, and inhaled corticosteroids – a prospective study. *Archives of Diseases in Childhood* 1996 **74** 497–501.
 - 44 Cooper C, Coupland C & Mitchell M. Rheumatoid arthritis,

- corticosteroid therapy and hip fracture. *Annals of the Rheumatic Diseases* 1995 **54** 49–52.
- 45 Michel BA, Bloch DA, Wolfe F & Fries JF. Fractures in rheumatoid arthritis – an evaluation of associated risk factors. *Journal of Rheumatology* 1993 **20** 1666–1669.
 - 46 Nilsen KH, Jayson MIV & Dixon ASTJ. Microcrystalline calcium hydroxyapatite compound in corticosteroid-treated rheumatoid patients: a controlled study. *British Medical Journal* 1978 **2** 1124.
 - 47 Reid IR & Ibbertson HK. Calcium supplements in the prevention of steroid-induced osteoporosis. *American Journal of Clinical Nutrition* 1986 **44** 287–290.
 - 48 Reid IR, King AR, Alexander CJ & Ibbertson HK. Prevention of steroid-induced osteoporosis with (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (APD). *Lancet* 1988 **i** 143–146.
 - 49 Reid IR, Heap SW, King AR & Ibbertson HK. Two-year follow-up of bisphosphonate (APD) treatment in steroid osteoporosis. *Lancet* 1988 **ii** 1144.
 - 50 Sambrook P, Birmingham J, Kelly P, Kempler S, Nguyen T, Pocock N & Eisman J. Prevention of corticosteroid osteoporosis – a comparison of calcium, calcitriol, and calcitonin. *New England Journal of Medicine* 1993 **328** 1747–1752.
 - 51 Lukert BP, Johnson BE & Robinson RG. Estrogen and progesterone replacement therapy reduces glucocorticoid-induced bone loss. *Journal of Bone and Mineral Research* 1992 **7** 1063–1069.
 - 52 Grey AB, Cundy TF & Reid IR. Continuous combined oestrogen/progestin therapy is well tolerated and increases bone density at the hip and spine in post-menopausal osteoporosis. *Clinical Endocrinology* 1994 **40** 671–677.
 - 53 Reid IR & Grey AB. Corticosteroid osteoporosis. *Bailliere's Clinical Rheumatology* 1993 **7** 573–587.
 - 54 MacDonald AG, Murphy EA, Capell HA, Bankowska UZ & Ralston SH. Effects of hormone replacement therapy in rheumatoid arthritis – a double blind placebo-controlled study. *Annals of the Rheumatic Diseases* 1994 **53** 54–57.
 - 55 Studd JWW, Savvas M & Johnson M. Correction of corticosteroid-induced osteoporosis by percutaneous hormone implants. *Lancet* 1989 **i** 339.
 - 56 Hall GM, Daniels M, Huskisson EC & Spector TD. A randomised controlled trial of the effect of hormone replacement therapy on disease activity in postmenopausal rheumatoid arthritis. *Annals of the Rheumatic Diseases* 1994 **53** 112–116.
 - 57 Reid IR, Wattie DJ, Evans MC & Stapleton JP. Testosterone therapy in glucocorticoid-treated men. *Archives of Internal Medicine* 1996 **156** 1173–1177.
 - 58 Need AG. Corticosteroids and osteoporosis. *Australia and New Zealand Journal of Medicine* 1987 **17** 267–272.
 - 59 Adami S, Fossaluzza V, Rossini M, Bertoldo F, Gatti D, Zamberlan N *et al.* The prevention of corticosteroid-induced osteoporosis with nandrolone decanoate. *Bone and Mineral* 1991 **15** 72–81.
 - 60 Grecu EO, Weinschelbaum A & Simmons R. Effective therapy of glucocorticoid-induced osteoporosis with medroxyprogesterone acetate. *Calcified Tissue International* 1990 **46** 294–299.
 - 61 Cundy T, Evans M, Roberts H, Wattie D, Ames R & Reid IR. Reduced bone density in women using depot medroxyprogesterone acetate for contraception. *British Medical Journal* 1991 **303** 13–16.
 - 62 Gallacher SJ, Fenner JAK, Anderson K, Bryden FM, Banham SW, Logue FC, Cowan RA & Boyle IT. Intravenous pamidronate in the treatment of osteoporosis associated with corticosteroid dependent lung disease – an open pilot study. *Thorax* 1992 **47** 932–936.
 - 63 Worth H, Stammen D & Keck E. Therapy of steroid-induced bone loss in adult asthmatics with calcium, vitamin D, and a diphosphonate. *American Journal of Respiratory Critical Care Medicine* 1994 **150** 394–397.
 - 64 Diamond T, McGuigan L, Barbagallo S & Bryant C. Cyclical etidronate plus ergocalciferol prevents glucocorticoid-induced bone loss in postmenopausal women. *American Journal of Medicine* 1995 **98** 459–463.
 - 65 Struys A, Snelder AA & Mulder H. Cyclical etidronate reverses bone loss of the spine and proximal femur in patients with established corticosteroid-induced osteoporosis. *American Journal of Medicine* 1995 **99** 235–242.
 - 66 Hahn TJ & Hahn BH. Osteopenia in patients with rheumatic diseases: principles of diagnosis and therapy. *Seminars in Arthritis and Rheumatism* 1976 **6** 165–188.
 - 67 Hahn TJ, Halstead LR, Teitelbaum SL & Hahn BH. Altered mineral metabolism in glucocorticoid-induced osteopenia. *Journal of Clinical Investigation* 1979 **64** 655–665.
 - 68 Dykman TR, Haralson KM, Gluck OS, Murphy WA, Teitelbaum SL, Hahn TJ *et al.* Effect of oral 1,25-dihydroxy-vitamin D and calcium on glucocorticoid-induced osteopenia in patients with rheumatic diseases. *Arthritis and Rheumatism* 1984 **27** 1336–1343.
 - 69 Bijlsma JWJ, Raymakers JA, Mosch C, Hoekstra A, Derksen RH, Ochipinti G *et al.* Effect of oral calcium and vitamin D on glucocorticoid-induced osteopenia. *Clinical and Experimental Rheumatology* 1988 **6** 113–119.
 - 70 Di Munno O, Beghe F, Favini P, Di Giuseppe P, Pontrandolfo A, Occhipinti G *et al.* Prevention of glucocorticoid-induced osteopenia: effect of oral 25-hydroxyvitamin D and calcium. *Clinical Rheumatology* 1989 **8** 202–207.
 - 71 Mulder H & Struys A. Intermittent cyclical etidronate in the prevention of corticosteroid-induced bone loss. *British Journal of Rheumatology* 1994 **33** 348–350.
 - 72 Van Cleemput J, Daenen W, Geusens P, Dequeker J, Van de Werf F & Vanhaecke J. Prevention of bone loss in cardiac transplant recipients – a comparison of bisphosphonates and vitamin D. *Transplantation* 1996 **61** 1495–1499.
 - 73 Adachi JD, Bensen WG, Bianchi F, Cividino A, Pillersdorf S, Sebaldt RJ, Tugwell P, Gordon M, Steele M, Webber C & Goldsmith CH. Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis – a 3 year follow-up. *Journal of Rheumatology* 1996 **23** 995–1000.
 - 74 Buckley LM, Leib ES, Cartularo KS, Vacek PM & Cooper SM. Calcium and vitamin D-3 supplementation prevents bone loss in the spine secondary to low-dose corticosteroids in patients with rheumatoid arthritis – a randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine* 1996 **125** 961–968.
 - 75 Bayley TA, Muller C & Harrison J. The long-term treatment of steroid osteoporosis with fluoride. *Journal of Bone and Mineral Research* 1990 **5** (suppl 1) S157–S161.
 - 76 Rizzoli R, Chevalley T, Slosman DO & Bonjour JP. Sodium monofluorophosphate increases vertebral bone mineral density in patients with corticosteroid-induced osteoporosis. *Osteoporosis International* 1995 **5** 39–46.
 - 77 Guaydier-Souquieres G, Kotzki PO, Sabatier JP, Bassecathalinat B & Loeb G. In corticosteroid-treated respiratory diseases, monofluorophosphate increases lumbar bone density – a double-masked randomized study. *Osteoporosis International* 1996 **6** 171–177.
 - 78 Meunier PJ, Briancon D, Chavassieux P, Edouard C, Boivin G, Conrozier T, Marcelli C, Pastoureaux P, Delmas PD & Casez JP. Treatment with fluoride: bone histomorphometric findings. In *Osteoporosis*, pp 824–828. Eds C Christiansen, JS Johansen & BJ Riis. Copenhagen: Osteopress, 1987.
 - 79 Rizzato G, Tosi G, Schiraldi G, Montemurro L, Zanni D & Sisti S. Bone protection with salmon calcitonin (sCT) in the long-term steroid therapy of chronic sarcoidosis. *Sarcoidosis* 1988 **5** 99–103.
 - 80 Luengo M, Picado C, Del Rio L, Guanabens M, Montserrat IM & Setoain J. Treatment of steroid-induced osteopenia with calcitonin in corticosteroid-dependent asthma. *American Review of Respiratory Disease* 1990 **142** 104–107.
 - 81 Montemurro L, Schiraldi G, Fraioli P, Tosi G, Riboldi A & Rizzato G. Prevention of corticosteroid-induced osteoporosis with salmon calcitonin in sarcoid patients. *Calcified Tissue International* 1991 **49** 71–76.
 - 82 Adams JS, Wahl TO & Lukert BP. Effects of hydrochlorothiazide

- and dietary sodium restriction on calcium metabolism in corticosteroid treated patients. *Metabolism* 1981 **30** 217–221.
- 83 Suzuki Y, Ichikawa Y, Saito E & Homma M. Importance of increased urinary calcium excretion in the development of secondary hyperparathyroidism of patients under glucocorticoid therapy. *Metabolism* 1983 **32** 151–156.
- 84 Yamada H. Long-term effect of 1 alpha-hydroxyvitamin D, calcium and thiazide administration on glucocorticoid-induced osteoporosis. *Nippon Naibunpi Gakkai Zasshi* 1989 **65** 603–614.
- 85 Caniggia A, Marchetti M, Gennari C, Vattimo A & Nicholis FB. Effects of a new glucocorticoid, oxazacort, on some variables connected with bone metabolism in man: a comparison with prednisone. *International Journal of Clinical Pharmacology* 1977 **15** 126–134.
- 86 Gray RES, Doherty SM, Galloway J, Coulton L, de Broe M & Kanis JA. A double-blind study of deflazacort and prednisone in patients with chronic inflammatory disorders. *Arthritis and Rheumatism* 1991 **34** 287–295.
- 87 Lo Cascio V, Bonucci E, Imbimbo B, Ballanti P, Tantarotti D, Galvanini G *et al.* Bone loss after glucocorticoid therapy. *Calcified Tissue International* 1984 **36** 435–438.
- 88 Gennari C & Imbimbo B. Effects of prednisone and deflazacort on vertebral bone mass. *Calcified Tissue International* 1985 **37** 592–593.
- 89 Loftus J, Allen R, Hesp J, David J, Reid DM, Wright DJ *et al.* Randomized, double-blind trial of deflazacort versus prednisone in juvenile chronic rheumatoid arthritis: a relatively bone-sparing effect of deflazacort. *Paediatrics* 1991 **88** 428–436.
- 90 Olgaard K, Storm T, van Wouern N, Daugaard H, Egfjord M, Lewin E *et al.* Glucocorticoid induced osteoporosis in the lumbar spine, forearm and mandible of nephrotic patients. A double-blind study on the high-dose long-term effects of prednisone versus deflazacort. *Calcified Tissue International* 1992 **50** 490–497.
- 91 Balsan S, Steru D, Bourdeau A, Grimberg R & Lenoir G. Effects of long-term maintenance therapy with a new glucocorticoid, deflazacort, on mineral metabolism and statural growth. *Calcified Tissue International* 1987 **40** 303–309.
- 92 Aicardi G, Milani S, Imbimbo B, Vignolo M, di Battista E, Gusmano R *et al.* Comparison of growth retarding effects induced by two different glucocorticoids in prepubertal sick children: an interim long-term analysis. *Calcified Tissue International* 1991 **48** 283–287.
- 93 Dimunno O, Imbimbo B, Mazzantini M, Milani S, Occhipinti G & Pasero G. Deflazacort versus methylprednisolone in polymyalgia rheumatica: clinical equivalence and relative antiinflammatory potency of different treatment regimens. *Journal of Rheumatology* 1995 **22** 1492–1498.
- 94 Weisman MH. Dose equivalency of deflazacort and prednisone in the treatment of steroid dependent rheumatoid arthritis. In *Proceedings of the 4th International Symposium on Osteoporosis*, p 515. Eds C Christiansen & B Riis. Copenhagen: 4th International Symposium on Osteoporosis, 1993.
- 95 Krogsgaard MR, Thamsborg G & Lund B. Changes in bone mass during low dose corticosteroid treatment in patients with polymyalgia rheumatica – a double blind, prospective comparison between prednisolone and deflazacort. *Annals of the Rheumatic Diseases* 1996 **55** 143–146.

Received 11 February 1997

Accepted 20 May 1997