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Glucocorticoid-induced osteoporosis

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Glucocorticoid drugs interact with bone metabolism at many levels, but their principal action is to reduce osteoblast number and bone matrix synthesis. Virtually all patients receiving glucocorticoids in doses above 5 mg per day lose bone, the amount lost being dependent on the cumulative steroid dose. The risk of fracture is also related to the individual's initial bone density, which in turn reflects race, sex, age, menopausal status, body weight, smoking and the nature of any underlying illness. Bone density measurement and personal fracture history are the best predictors of future fracture risk. Steroid-induced bone loss is reversible, so measures to minimize the systemic steroid dose or to withdraw these drugs altogether should be pursued no matter how long an individual has been using them. Increasing the calcium intake to 1.5 g per day, encouraging them to stop smoking and take more exercise, and treating any vitamin D deficiency are sensible measures in all patients. In those at high risk, bisphosphonates are the best documented interventions, although sex hormone replacement is also effective and can be used alone or in addition to bisphosphonates.

Key words: corticosteroid; prednisone; prednisolone; Cushing's syndrome; fracture; bone density; bisphosphonates; vitamin D; calcitonin; fluoride.

It is now 50 years since the introduction of glucocorticoids into clinical practice, and their continued widespread use attests to their unrivalled efficacy in a number of major illnesses, including obstructive respiratory disease and inflammatory conditions such as rheumatoid arthritis, temporal arteritis and inflammatory bowel disease. They also continue to have a major role in the management of organ transplantation. Their substantial therapeutic efficacy is counterbalanced by a number of major side-effects that sometimes produce morbidity comparable to that of the original illness. One of these is the development of osteoporosis. An emphasis on this particular problem is most appropriate at this time, since developments in both diagnostics and therapeutics have made it possible to predict those who will have fractures and to intervene effectively to prevent this eventuality. Thus, the assessment of osteoporosis and the appropriate use of interventions have moved from the research agenda to now being major responsibilities incumbent on any doctor prescribing glucocorticoid drugs.

PATHOGENESIS

Because of the widespread distribution of the glucocorticoid receptor, these agents are able to impact on bone and calcium metabolism at many levels (Figure 1). These effects have recently been reviewed in detail.[1]

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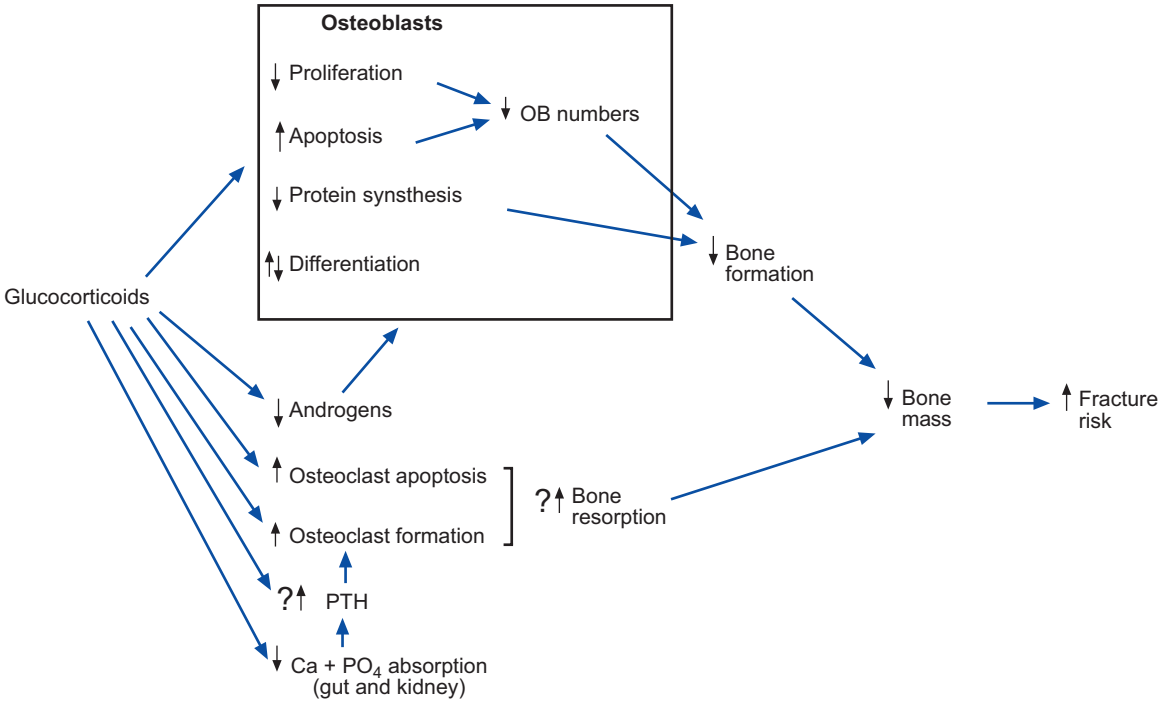

Figure 1. Mechanisms by which glucocorticoids result in bone loss. Copyright I.R. Reid; used with permission.

Osteoblasts

Glucocorticoids modulate the expression of genes (including that for bone morphogenic protein-6) in osteoblast precursor cells to produce a more differentiated osteoblastic phenotype.[2,3] In mature osteoblasts, however, they inhibit both cell proliferation and matrix synthesis, and this is the predominant effect observed in vivo since it is favoured by high hormone concentrations and long exposure periods. This effect is probably also the result of the direct regulation of genes by glucocorticoids, target genes including those for type I collagen, osteocalcin and the insulin-like growth factors and their binding proteins.[4] In addition, it now appears that glucocorticoids hasten the apoptotic demise of both osteoblasts and osteocytes, further contributing to reduced bone formation.[5,6] These effects are seen in both animal and human histomorphometric studies, in which the rate of bone production within each bone-modelling unit and the duration of activity of each unit are reduced. Assessments of biochemical markers of bone formation consistently show evidence of reduced bone formation (Table 1).

Table 1. Prospective studies of the effects of glucocorticoids on biochemical markers of bone turnover.

	Study reference					
	Prummel et al[105]	Morrison et al[106]	Cosman et al[107]	Lems et al[108]	Lane et al[19]	Wolthers et al[109]
Underlying disease	EGO	COAD	MS	RA	Asthma	Nil
Treatment duration	12 weeks	4 weeks	5 weeks	8 days	5 days	3 days
Drug	Pred	Pred	Pred	Dexa	Pred	Pred
Daily dose	40 mg	20 mg	1 g → 5 mg	75 mg	40 mg	40 mg
Formation markers						
Osteocalcin	↓	→	↓ ↓	↓	↓	
Total ALP	↓	↓		→	↓	
Bone ALP	↓ (NS)				→	
PICP				↓		↓
Resorption markers						
ICTP				↓		↓
Pyridinoline			→	↓		→
Deoxypyridinoline				↓	→	→
Hydroxyproline	→	↑	→	→		
TRAP			↑		→	
Urine calcium	↑		↑	→		

EGO = euthyroid Grave's ophthalmopathy; COAD = chronic obstructive airways disease; MS = multiple sclerosis; RA = rheumatoid arthritis; Pred = (methyl)prednis(ol)one; Dexa = dexamethasone. NS, not significant.

Osteoclasts

Data on the effects of glucocorticoids on osteoclasts are contradictory. There is evidence that glucocorticoids increase osteoclast formation from precursor cells in bone marrow, possibly as a result of the reduced osteoblast production of osteoprotegerin and the increased production of RANKL.[7] However, glucocorticoids also increase the apoptosis of mature osteoclasts. These opposing effects may account for the findings in organ culture that glucocorticoids can either increase or decrease bone resorption,

depending on the culture conditions.[8] In organ culture, glucocorticoid effects may be contributed to by the inhibition of production of local osteolytic cytokines such as interleukins-1 and -6, tumour necrosis factor and leukaemia inhibitory factor, and their stimulation of macrophage-colony stimulating factor production by osteoblasts.

Animal and human studies are also difficult to interpret, showing an increase in the eroded bone surface but a decrease in the number of osteoclasts. These findings could be accounted for by a reduced rate of recruitment of osteoblasts to the sites at which bone has been resorbed, leaving eroded surfaces unfilled for a greater than normal time. Thus, there is probably not an increased rate of bone resorption, and most of the human studies of biochemical markers of bone resorption would be consistent with this conclusion (see Table 1 above).

Intestinal and renal handling of calcium and phosphate

Studies have consistently demonstrated an inhibition of calcium absorption associated with glucocorticoid treatment. This is not mediated by changes in vitamin D metabolites and is therefore likely to represent a direct effect on the calcium transport system in the small intestine.

Within weeks of glucocorticoid treatment, there is a substantial rise in urine calcium excretion, which appears to be caused by a direct inhibition of the tubular resorption of calcium. There is also evidence of malabsorption of phosphate in both the gut and renal tubule associated with glucocorticoid use.

Vitamin D

There is little evidence that changes in vitamin D metabolism contribute significantly to the development of glucocorticoid osteoporosis. Prospective studies of patients and normal subjects beginning glucocorticoid therapy have shown no changes in the serum level of 25-hydroxyvitamin D or 24,25-dihydroxyvitamin D, but a significant increase in serum 1,25-dihydroxyvitamin D has been observed 2–15 days after the initiation of therapy. This is likely to be secondary to changes in parathyroid hormone and/or serum phosphate concentration. There is also no evidence for glucocorticoid effects on the concentration of vitamin D-binding protein.

Parathyroid hormone

Hyperparathyroidism has been inconsistently demonstrated in human and animal studies spanning durations of glucocorticoid use from minutes to years. Some cross-sectional studies of patients receiving chronic glucocorticoid therapy show an elevation of parathyroid hormone levels 50–100% above those of control subjects, although others show no effect. Glucocorticoids appear directly to stimulate parathyroid hormone secretion, although in vivo calcium malabsorption in both the gut and the renal tubule probably also contributes.

Sex hormones

Sex hormones are important regulators of bone metabolism, hypogonadism in either sex being associated with the development of osteoporosis. Glucocorticoids acutely depress the plasma level of testosterone in men, and their chronic use is associated with a dose-dependent reduction in free testosterone concentration of approximately

50%.[9] These changes result from both an inhibition of gonadotropin secretion and a reduction in the number of gonadotropin-binding sites in the testis. High-dose glucocorticoid therapy is associated with oligomenorrhoea in women, suggesting a similar effect on the pituitary–gonadal axis.

EFFECTS ON BONE MINERAL DENSITY

Within hours of glucocorticoid administration, there is a fall in the circulating level of osteocalcin, a bone matrix protein produced by osteoblasts. This change in osteoblast activity is followed by a fall in bone mass that is maximal over the first few months of therapy. The losses may be considerable and depend to some extent on the method of their estimation. In a study assessing bone loss using biopsies, cancellous bone volume decreased by almost 30%, most of this loss occurring over the first 6 months.[10] Patients in this study were treated with 10–25 mg per day of prednisone. Laan et al[11] demonstrated an average loss of 8% of cancellous bone density and 2% of cortical bone density in the lumbar spine over a 20-week period in response to treatment with a mean dose of prednisone of 7.5 mg per day.

An increased rate of bone loss persists, even in patients who have already been taking steroids for some years. Saito et al[12] demonstrated a rate of loss two to three times higher than that of control subjects in older men and women who had already been using steroids for a mean period of 2 years. Continuing bone loss is particularly likely in subjects requiring more than 10 mg per day of prednis(ol)one.[13] As a result, bone mineral density in glucocorticoid-treated subjects studied cross-sectionally is related to both the duration and dose of treatment[13–15], as well as to factors such as body weight and age that influence pre-treatment bone mineral density.[16]

Cross-sectional assessments of bone mineral density in glucocorticoid-treated patients show values extending from the middle of the age-appropriate normal range to substantially below it. The fact that a number of glucocorticoid-treated patients thus have a normal bone mineral density is sometimes interpreted as indicating that some individuals are resistant to the osteopenic effects of glucocorticoids. This is theoretically possible since there are polymorphisms of the glucocorticoid receptor that might result in a difference between subjects in sensitivity to these hormones.[17] There is, however, little clinical evidence that this is of practical importance, and the limited number of prospective data that are available indicate that virtually all subjects lose bone.[11,18]

Biochemical studies have also failed to identify a subgroup of glucocorticoid-treated patients who do not show a suppression of markers of osteoblast activity.[19] Therefore, the fact that some glucocorticoid-treated patients have bone mineral density values within the normal range is probably a reflection of the fact that the mean value has been displaced downwards by an amount that is less than the width of the normal range. In anteroposterior dual-energy X-ray absorptiometry (DXA) scans of the lumbar spine, for example, the normal range extends from 80% to 120% of the mean normal value. An average bone loss of 20% in patients receiving glucocorticoids results in the range in these subjects extending from 60% to 100% of the mean normal value.[20] The fact that bone mineral density in glucocorticoid-treated patients remains normally distributed with a standard deviation the same as that of normal subjects indicates that a uniform reduction in bone density must have occurred and rules out the existence of a significant number of subjects who do not undergo any bone loss when taking these drugs long term.

Cross-sectional studies of patients treated for a period of 5 years show that the integral bone mineral density of the lumbar spine and proximal femur is about 20% below control values.[20] However, the more rapid loss of cancellous bone results in decrements approaching 40% when lumbar spine mineral density is assessed by quantitative computed tomography (QCT)[13] or DXA in the lateral projection.[21] The more rapid loss of cancellous bone is a reflection of the greater surface-to-volume ratio of cancellous bone. Since bone remodelling takes place only at bone surfaces, cancellous bone responds more rapidly than cortical bone to either positive or negative changes in bone balance.

The bone loss induced by glucocorticoids is substantially reversible following the withdrawal of these drugs. Two prospective studies have demonstrated a re-accumulation of bone mineral density over approximately the same timespan as its loss occurred.[11,18] Substantial increases in bone mineral density have been reported after the cure of Cushing's syndrome[22,23], and we have demonstrated that bone mineral density is normal in subjects cured of Cushing's syndrome for a mean period of 9 years.[24] The alternate-day administration of the glucocorticoids, however, does not diminish bone loss.[25,26]

EFFECTS ON FRACTURE INCIDENCE

Because glucocorticoids have their greatest effect on cancellous bone, fractures are most common in regions of the skeleton that are predominantly cancellous, such as the vertebral bodies and ribs. Approximately one third of patients have evidence of vertebral fractures after 5–10 years of glucocorticoid treatment[27–32], although this can be very much higher in older men with chronic obstructive respiratory disease (over 60%), in whom the risk of fracture without glucocorticoid use is already quite substantial.[33] The risk of hip fracture is also increased nearly threefold in patients taking glucocorticoids.[34] Fracture risk is related to the duration of glucocorticoid use, age, body weight (inversely) and female sex.[35] In a recent prospective study, Adachi et al[36] observed new vertebral fractures in 3 out of 25 men, zero out of 8 pre-menopausal women and 7 out of 32 post-menopausal women treated with glucocorticoids over a period of 12 months.

LOCALLY ADMINISTERED GLUCOCORTICOIDS

In some conditions, it is now possible to administer glucocorticoids locally, thereby reducing the systemic side-effects. There is, however, usually some systemic absorption, and this is emphasized by the recent reports that inhaled glucocorticoids result in growth retardation in children[37,38] and the development of cataracts in adults.[39] Both beclomethasone and budesonide can affect osteoblast markers in doses as low as 800 μg per day, although fluticasone appears to have lesser effects on bone when given in doses with the same anti-asthmatic effect.[40] Some cross-sectional studies have indicated that bone mineral density is reduced in those using inhaled glucocorticoids (reviewed in reference 38), but this has not been the finding of the small number of prospective studies available[41], suggesting that the cross-sectional studies are confounded by the effects of past oral glucocorticoid use or by the underlying disease. A recent randomized controlled trial of fluticasone 500 μg twice daily or placebo showed an almost identical change in bone mineral density in the two

groups over a 2-year period.[42] While caution remains appropriate, locally administered glucocorticoids are to be preferred to systemic preparations because their ratio of therapeutic benefits to bone loss is substantially greater.

ASSESSMENT OF BONE LOSS

Most individuals using glucocorticoid drugs in doses greater than the equivalent of prednisolone 5 mg per day will experience bone loss and may be at risk of fractures. The clinical risk factors cited above are of some value in identifying such patients but are only poorly correlated with bone mineral density[43], which should therefore be measured directly in patients requiring these doses for more than a few months.

Since vertebral bodies are a common site of bone loss and fracture, they are the logical place at which to measure bone mineral density. Techniques that focus on the vertebral body and exclude the cortical bone of the posterior processes (such as lateral DXA scanning or QCT) are likely to be more sensitive in detecting glucocorticoid-induced bone loss.[21,44] When selecting a method of bone mineral density measurement in an individual patient, however, other factors need to be considered. The presence of vertebral deformities, vertebral osteophytes or aortic calcification can artefactually elevate spinal bone mineral density values. Lateral scans of the vertebral bodies, particularly in the decubitus position, are significantly less precise than anteroposterior scans and are therefore less satisfactory for following a change in bone mass prospectively.

In patients in whom there is marked osteophytosis or scoliosis of the spine, proximal femoral densitometry should be carried out. Ward's triangle is the part of the proximal femur with the highest proportion of cancellous bone and generally shows the most marked reduction in glucocorticoid-treated patients[20] but, like the lateral spine scan, has a low precision. It is therefore unsuitable for monitoring a patient longitudinally, and the femoral trochanter or the 'total femur' region is the most suitable for this purpose.

Ultrasound of the heel has also been investigated as a method of assessing bone loss in glucocorticoid-treated patients.[45–47] The data are very limited at the present time but suggest that it is at least as sensitive as femoral or anteroposterior spine scans using DXA.[45,47] The calcaneus would be expected to be a useful site for assessing glucocorticoid-induced bone loss because it is rich in cancellous bone. Confirmation of these findings is required before ultrasound can be used in routine clinical practice for such assessments.

The clinical value of biochemical markers of bone turnover in predicting bone loss in glucocorticoid-treated subjects has not been established. Osteocalcin is very sensitive to glucocorticoid administration, the effects being dose related[48], but it is no more predictive of subsequent bone loss than is the dose.[49] In most studies, base-line levels of osteocalcin and other markers, or their change in the early months of therapy, have not been found to relate to subsequent bone loss in either adults[13,50] or children.[51]

In a study of patients undergoing heart transplantation, Shane et al[52] showed some relationship between bone loss and serum osteocalcin, urinary deoxypyridinoline, urinary hydroxyproline and urinary calcium levels. However, these relationships varied from one skeletal site and one time point to another, accounting for less than 10% of the variance in rate of bone loss. This study also suggested that a low serum level of either 25-hydroxyvitamin D or testosterone 3 months after transplantation

was related to more rapid bone loss, although the predictive value was also relatively low. Sambrook et al have reported similar findings[53] in their cardiac transplant patients, in whom a change in bone mass was related to the concentration of both osteocalcin (directly) and testosterone (inversely). Findings in transplantation studies may not be generalizable to monotherapy with glucocorticoids, since transplant patients usually receive other agents, for example cyclosporin, which increase bone turnover and thus change the relationship between markers and bone loss.

INTERVENTIONS TO INCREASE BONE MASS

Most of the therapies used in post-menopausal osteoporosis have been assessed in glucocorticoid osteoporosis. Their efficacy in the former context is, however, not necessarily generalizable, since the pathogenesis differs. Furthermore, the size and number of studies carried out in glucocorticoid osteoporosis are both considerably less than in post-menopausal osteoporosis, so the evidence for the anti-fracture efficacy of most agents is absent (Table 2). Some studies distinguish between the use of anti-osteoporotic therapies at the time of first use of glucocorticoids and the treatment of established osteoporosis in those who have already received long-term glucocorticoid treatment. In general, this distinction is not important since the efficacy of most agents is similar in both situations. The timing of anti-osteoporotic therapy should be determined by an individual's absolute fracture risk at any point in time.

Table 2. Quality of evidence for the efficacy of interventions in glucocorticoid osteoporosis.

Intervention	Spine bone density	Hip bone density	Vertebral fracture	Non-vertebral fracture
Calcium	–	–	–	–
Calcium + vitamin D	C	C	–	–
HRT	D	D	–	–
Testosterone	B	–	–	–
Etidronate	A	A	B*	–
Alendronate	A	A	B*	–
Risedronate	A	A	A	–
Calcitriol	C	–	–	–
Alphacalcidol	A	C	–	–
Fluoride	A	–	–	–
Calcitonin	B	–	–	–

A = Positive evidence from one or more, adequately powered, randomized controlled trials.
B = Positive evidence from smaller non-definitive randomized controlled trials.
C = Inconsistent results from randomized controlled trials.
D = Positive results from observational studies.
– = Efficacy not established.
* = Seen only in post-menopausal women; *post hoc* analysis.

The general measures that should be considered in all osteoporotic patients (e.g. mobilization, attention to nutrition, cessation of smoking and moderation of alcohol intake) are appropriate in those receiving glucocorticoids whatever their bone density. In those with a higher risk of fracture, pharmacological intervention is usually also necessary. The therapeutic options are as follows.

Calcium and vitamin D

Calcium and vitamin D have been used for several decades as an empirical therapy for osteoporosis of various aetiology. Their combined use in trials, however, potentially obscures their relative contributions to any beneficial effects. There are extensive observational data on the effect of calcium supplementation on glucocorticoid-induced bone loss in that the 'control' groups in trials of most other agents have been given calcium.[54,55] These data indicate that considerable bone loss still occurs despite calcium supplementation. Calcium does, however, reduce the biochemical indices of bone resorption in glucocorticoid-treated patients[56], and hydroxyapatite tablets have been shown to slow forearm bone loss in one study.[57]

Two studies of calcium and vitamin D combinations have recently been reported. Buckley et al studied patients with rheumatoid arthritis receiving low-dose prednisone who were randomized to receive placebo or calcium 500 mg per day plus vitamin D 500 IU per day.[58] Those receiving calcium and vitamin D showed a 2% more positive change in bone mineral density that did those receiving placebo. The vitamin D status of the study subjects was not assessed. In contrast, Adachi et al[59] failed to show any benefit on lumbar spine bone mineral density from the use of calciferol 50 000 u per week plus calcium 1000 mg per day in a randomized controlled trial over 3 years.

Thus, the case for either calcium or vitamin D having a specific role in the management of steroid osteoporosis is not compelling. It currently seems reasonable to provide calcium supplementation to those whose dietary intake is less than 1–1.5 g per day (i.e. 4–6 servings of dairy products) and in whom there are no contra-indications (e.g. renal calculi). There is increasing evidence of deleterious effects on the skeleton of vitamin D deficiency in the frail elderly population, and this is also likely to be relevant to frail glucocorticoid-treated patients who are seldom outdoors. Therefore, the assessment of vitamin D status (by a measurement of serum 25-hydroxyvitamin D) and, where necessary, supplementation with vitamin D itself (e.g. calciferol 500–1000 u per day or 20 000–50 000 u per month) is appropriate for glucocorticoid-treated patients at risk.

Vitamin D metabolites

The case for using vitamin D metabolites to treat osteoporosis is mixed, since these agents increase both intestinal calcium absorption and bone resorption, thus potentially accelerating bone loss as well as placing the patient at risk of hypercalcaemia. This balance of the potential benefits and risks may be different for different agents and doses.

Trials in this area have recently been reviewed.[60] Two small studies have demonstrated benefit from the use of 25-hydroxyvitamin D, but this agent is not widely available.[61,62] Since much of a dose of calciferol is converted to 25-hydroxyvitamin D, it is not clear that the effects of these two agents would be expected to be different.

Calcitriol has been assessed in several randomized controlled trials. Dykman et al[63] found no difference between calcitriol 0.4 μg per day and placebo in their effects on forearm bone mineral density. Sambrook et al[55] have reported a large, 1-year study in which patients starting glucocorticoid therapy were randomly assigned to receive calcium, calcium plus calcitriol (mean dose 0.6 μg per day) or these two agents combined with calcitonin. 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 of reduced bone loss in the proximal femur (3% in all groups).

A recent large trial over 3 years in cardiac transplant patients showed no effect on lumbar spine bone mineral density of calcitriol 0.25 μg per day.[64] A trial comparing the use of calcitriol 0.5 μg per day with hormone replacement therapy in hypogonadal young women with systemic lupus erythematosus showed a progressive bone loss in those taking the vitamin analogue in comparison with an increase in density observed in those receiving hormones (the between-group difference at the spine being 3.7% at 2 years).[65] There was also a significant difference between groups at the distal radius.

Alphacalcidol has been studied by Braun et al, who demonstrated a beneficial effect at a dose of 2 μg per day on cancellous bone volume over a 6-month period. Following cardiac transplantation, alphacalcidol has been shown to slow but not completely prevent femoral neck and lumbar spine bone loss.[66] A similar attenuation of lumbar spine bone loss has been reported in a predominantly non-transplant population with the use of alphacalcidol 1 μg per day, although femoral bone mineral density was not measured in this study.[67] In a population of patients with established glucocorticoid osteoporosis, Ringe et al have shown a beneficial effect at the lumbar spine (2.5% between groups at 3 years) of alphacalcidol 1 μg per day in comparison with calciferol plus calcium supplements.[68] There was no significant effect on the proximal femur. Thus, there is some consistency in the results with this particular agent. A 2-year study failed to show any benefit from the use of dihydrotachysterol.[69]

The variability of outcomes with the various agents in this class make it difficult to generalize with respect to the use of vitamin D metabolites in the management of glucocorticoid osteoporosis. The most consistent data are for alphacalcidol, although its effect is generally less than that of the bisphosphonates. The best use of these metabolites may be as adjunctive therapy to either sex hormone replacement or bisphosphonates in patients with severe glucocorticoid osteoporosis, or as a second-line therapy in patients for whom these other agents are not acceptable.

Bisphosphonates

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 differences between individual bisphosphonates are their route of administration, their side-effects and their anti-resorptive potency, although most of the newer agents appear to achieve a comparable maximal inhibition of bone resorption. Bisphosphonates were originally used in glucocorticoid osteoporosis because their inhibition of bone resorption offered the potential to redress directly the imbalance between bone formation and resorption. It has recently been demonstrated in vitro that they reverse the increase in osteocyte and osteoblast apoptosis caused by glucocorticoids, so they may have a more specific role in this condition. Their use in glucocorticoid osteoporosis has recently been reviewed.[70]

The efficacy of the bisphosphonates was first demonstrated in the treatment of glucocorticoid osteoporosis.[54] In this randomized controlled trial, there was a 19% increase in the mineral density of the cancellous bone of the lumbar spine after 12 months' treatment with pamidronate, in comparison with a 9% decrease in those receiving placebo. There were smaller but statistically significant benefits in the cortical bone area of the metacarpals. In those patients proceeding to a second year of therapy, the gain in bone mineral density was maintained, whereas there was a progressive loss in the placebo group. Oral pamidronate is not widely available, but

three monthly intravenous infusions (30 mg) of this drug appear to be comparably effective.[71,72]

There are a number of studies showing that cyclic etidronate is an effective therapy in glucocorticoid-treated subjects. A large randomized controlled trial of etidronate has now been reported[36] and demonstrated a prevention of bone loss in both the lumbar spine and proximal femur in patients recently started on steroid treatment. Furthermore, it suggested that etidronate reduced the fracture rate by 50% and that height loss was also diminished.

A similar trial of alendronate has recently been reported.[73] This study included those already long established on glucocorticoid treatment as well as those just commencing it, and again demonstrated a beneficial effect on bone mineral density throughout the skeleton for doses of 5 mg per day and 10 mg per day, although the higher dose tended to be more effective. Benefit was seen in men, pre-menopausal women, and post-menopausal women whether or not receiving hormone replacement therapy. A gain in bone mass occurred irrespective of the duration of previous glucocorticoid use, and no adverse effects on bone histomorphometry were demonstrated.[74] The vertebral fracture rate was reduced by about half in those on alendronate, although this was only statistically significant among the post-menopausal women. Two further studies have demonstrated the effectiveness of alendronate in glucocorticoid-treated patients with sarcoidosis[75] and in patients with Cushing's syndrome.[76]

The newer bisphosphonate risedronate has now been evaluated in both the prevention and treatment of glucocorticoid osteoporosis.[77,78] The change in bone mineral density (with respect to placebo) was comparable to changes seen with etidronate and alendronate, but data from pooling the two studies indicated a more than 50% reduction in the number of fractures in the first year of treatment.

All bisphosphonates are very insoluble and therefore have a low oral bio-availability. To achieve benefit from oral dosing, they must be taken fasting with water at least 30 minutes before food and separated by some hours from the ingestion of mineral supplements (such as calcium or iron) or antacids. Rarely, they cause gastrointestinal irritation, alendronate being associated with oesophageal erosions (in those with gastro-oesophageal reflux) and etidronate with diarrhoea.

Of the various agents investigated to date, the bisphosphonates have produced the most consistently positive results on bone mineral density in glucocorticoid-treated subjects and the only evidence of a reduced fracture rate. They can be used in virtually all glucocorticoid-treated patients, including the young and sex hormone-replete.

Sex hormones

Oestrogen and testosterone have been used for a number of years in steroid-treated patients, not because they were thought specifically to interfere with the actions of glucocorticoids, but as a treatment for co-existing sex hormone deficiency. Recently, however, in vitro evidence has been presented suggesting that oestradiol reverses the apoptosis induced by dexamethasone.[5] This suggests that sex hormones might have a specific anti-glucocorticoid effect, although there is little clinical evidence of this since the magnitude of the increase in bone density they produce in glucocorticoid-treated patients is comparable to that seen in patients not taking glucocorticoids.[79–81] A role for sex hormone replacement in those without demonstrable deficiency has thus not been established.

Anabolic steroids, which are androgens modified to reduce their virilizing effects, have also been used for treating glucocorticoid-induced osteoporosis. They would

seem to have little place in the management of men, in whom they are likely further to reduce testosterone levels and in whom testosterone itself can be used if a deficiency is demonstrable. Their use in women is associated with a beneficial effect on bone mass but also with virilizing side-effects in almost one half of treated patients. Of these adverse effects, deepening of the voice is of particular concern since it is often irreversible.

Fluoride

The fluoride ion is a potent osteoblast mitogen capable of producing a sustained gain in lumbar spine bone mineral density when used long term. This unique beneficial effect is counterbalanced by its interference with the normal mineralization of bone when present in bone crystal at a high concentration. These opposing effects have made it difficult to translate fluoride's beneficial effects on bone mass into a reduced fracture incidence.

There is now clear evidence that fluoride increases spinal bone mineral density[82–85] and cancellous bone volume of the iliac crest[86] in glucocorticoid-treated subjects. However, its anti-fracture efficacy in this context remains to be established, and it should not be used as a first-line agent in glucocorticoid osteoporosis. Its cautious use may be appropriate as an adjunctive therapy in patients with severe bone loss.[87]

Calcitonin

Calcitonin acts via specific receptors on osteoclasts, reducing bone resorption. It has been used in some countries for the management of post-menopausal osteoporosis, although its effectiveness is generally less than that of hormone replacement therapy or the bisphosphonates. There have now been several controlled trials in glucocorticoid-treated subjects suggesting that it slows bone loss. Thus, Rizzato et al[88] 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[89] found a more modest difference between treatment groups – an increase in spinal bone density of 4% in those receiving calcitonin versus a decrease of 2.5% in the control group over a 12-month period.

Similar results using intranasal calcitonin have been reported by Montemurro et al[90] and by Adachi et al.[91] In the latter study, 31 patients starting glucocorticoid therapy for polymyalgia rheumatica were randomized to receive intranasal calcitonin 200 IU daily or placebo over a 12-month period. Mean spinal bone mineral density changed from 1.11 g/cm^2 to 1.08 g/cm^2 in the placebo group and from 1.06 g/cm^2 to 1.04 g/cm^2 in those receiving calcitonin. These results are statistically different, but the clinical significance of such a difference must be marginal. In the proximal femur, the between-groups trend was of similar magnitude but in the opposite direction, and in the total body scans the two groups responded identically. Thus, the clinical utility of intra-nasal calcitonin must remain in doubt, and calcitonin injections generally have a low acceptability to patients.

Parathyroid hormone

Parathyroid hormone is the focus of much attention in post-menopausal osteoporosis because of the substantial increase in axial bone density it has been shown to produce, particularly when administered intermittently in combination with an anti-resorptive

agent. This effect has now been demonstrated in post-menopausal women receiving glucocorticoid therapy and sex hormone replacement in a randomized controlled trial carried out over 12 months, in which an 11% increase in spine density was found.[92] Parathyroid hormone is not yet available, and some concerns regarding its safety have yet to be resolved.

Bone-sparing glucocorticoids

Deflazacort is a derivative of prednisolone that has been suggested to have a less deleterious effect on bone than prednisolone itself. This has been found with respect to hypercalciuria[93,94], calcium malabsorption in the intestine[93], bone loss[95–99] and growth retardation in children.[100,101] All these studies were, however, based on an assumption that the potency of prednisone relative to deflazacort was 1.2. There has recently been a re-examination of this question, with the finding that the relative potency is really 1.4–1.8.[102,103] 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 over-estimated in the past and demonstrated no bone-sparing effect of this agent compared with prednisone when used in a therapeutically equivalent dose.[104]

TREATMENT DECISIONS

The selection of a bone mineral density value at which intervention becomes appropriate is arbitrary and depends to some extent on the cost and potential side-effects of the available interventions. In the absence of evidence on which to base guidelines, it is reasonable to follow the practice established in post-menopausal osteoporosis and offer treatment to those whose bone density is more than 1–2 standard deviations below the young normal mean value. In an individual beginning glucocorticoid therapy, it can be predicted that the bone mineral density will drop a further 1–2 standard deviations below its current level in the first year of treatment, and this should be factored into the decision-making process. A past history of fracture after minimal trauma is also a major reason for weighting the balance in favour of intervention, since it implies that the individual's skeleton is already of marginal adequacy to withstand the trauma of daily living.

Figure 2 sets out an approach to both the evaluation of a steroid-treated patient and the making of therapeutic decisions, these being summarized as 'Practice Points' in Table 3. The optimization of dietary and lifestyle variables is applicable to all subjects receiving steroids. In those whose bone density is at the lower end of the young normal range, intervention with a single agent is appropriate, usually sex hormone replacement (in those with demonstrable deficiency) or a bisphosphonate. Since the therapeutic efficacy of these agents is comparable, the choice is based on a consideration of the patient's other medical problems, the possible side-effects and the cost. In a patient with marked bone loss, these agents can be combined with each other and/or with other interventions such as alphacalcidol or fluoride. The use of such combination regimens results in a substantial increase in bone density.

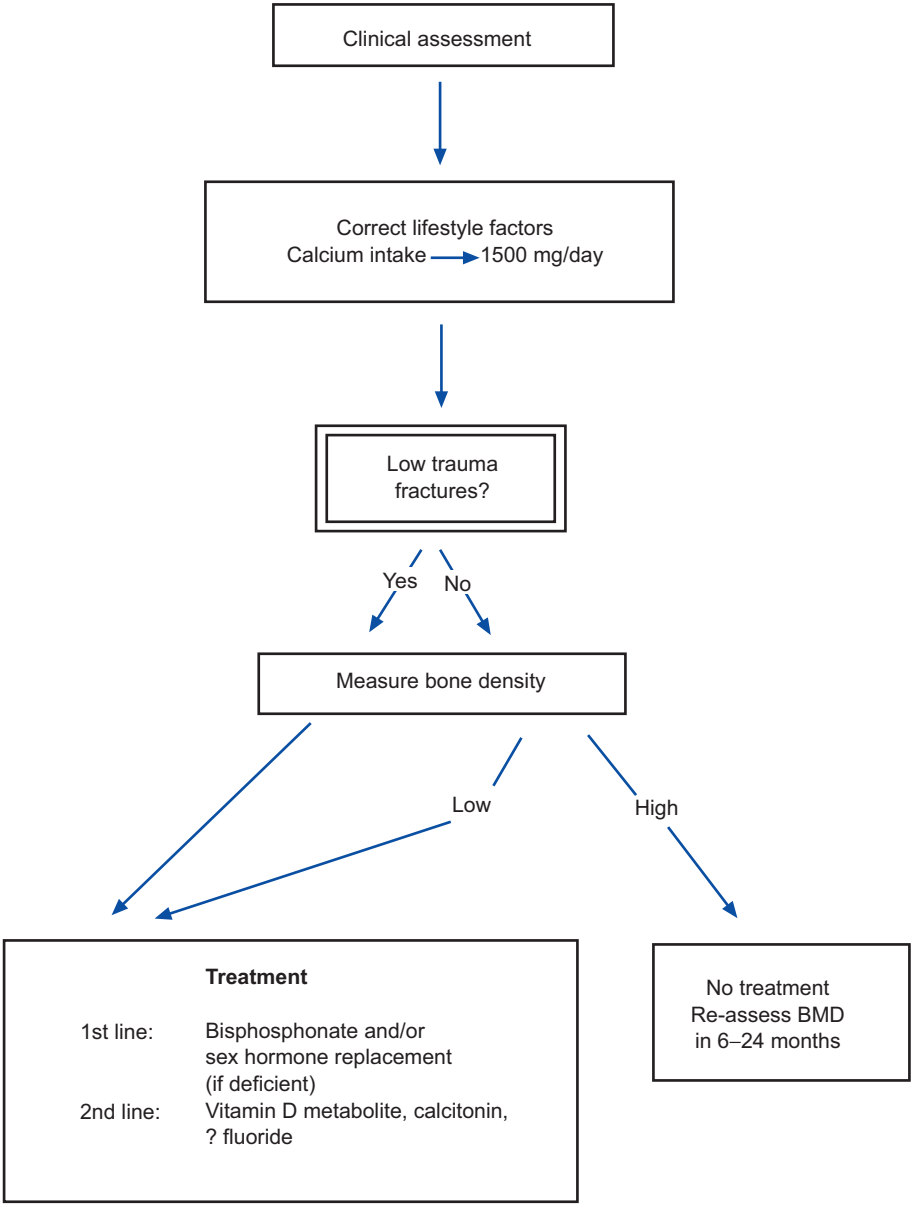

Figure 2. Flow chart for the evaluation and treatment of osteoporosis in patients receiving glucocorticoid therapy. Copyright I.R. Reid; used with permission.

RESEARCH AGENDA

The paucity of high-quality data on the anti-fracture efficacy of the available therapeutic agents, as highlighted in Table 2 above, points to the need for further large-scale clinical trials. Advances in the understanding of the molecular mechanisms

Table 3. Practice points.

- Virtually all patients receiving glucocorticoids in a dose of above 5 mg per day lose bone
- **The risk of fracture** is dependent on cumulative steroid dose and initial bone density, which will depend on race (being lowest in Europeans and Asians), sex, age, menopausal status, body weight, smoking and history of chronic inflammatory illness
- **Bone mineral density measurement** (e.g. by dual-energy X-ray absorptiometry at the spine) should be carried out in all patients receiving long-term steroids. Those with values in the lower third of the young normal range should be offered pharmacological bone protection
- A **history of fracture** after minimal trauma is an independent indication for intervention
- **Bisphosphonates** are the best-documented interventions
- **Sex hormone replacements** are also effective and can be used as the sole therapy or in addition to bisphosphonates
- **The serum 25-hydroxyvitamin D** concentration should be measured and supplementation with calciferol (50 000 units per month or 400–1000 units per day) provided if necessary
- Steroid-induced **bone loss is reversible**, so measures to minimize the systemic steroid dose or to withdraw these drugs altogether should be continued no matter how long an individual has been using them
- Increasing the calcium intake to 1.5 g per day, stopping smoking and encouraging exercise are sensible adjunctive measures

of action of glucocorticoids offer the possibility of dissociating their anti-inflammatory effects from their deleterious effects on bone. This is currently a long way from being a clinical reality, but it could eventually eliminate the problem of glucocorticoid osteoporosis altogether.

CONCLUSION

The availability of effective interventions in this condition places a responsibility on any prescriber of glucocorticoids to assess fracture risk in patients and to provide prophylaxis against bone loss. The widespread adoption of this strategy will result in many fewer of those patients receiving glucocorticoids having to accept the morbidity of multiple fractures on top of that of their other medical conditions.

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