

Bone loss and glucocorticoid therapy in patients with respiratory disease

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Introductory article

Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis

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Background. Osteoporosis is a common complication of long-term glucocorticoid therapy for which there is no well-proved preventive or restorative treatment. **Methods.** We carried out two 48-week, randomized, placebo-controlled studies of two doses of alendronate in 477 men and women, 17–83 years of age, who were receiving glucocorticoid therapy. The primary end point was the difference in the mean percent change in lumbar-spine bone density from base line to week 48 between the groups. Secondary outcomes included changes in bone density of the hip, biochemical markers of bone turnover, and the incidence of new vertebral fractures. **Results.** The mean (\pm SE) bone density of the lumbar spine increased by 2.1 ± 0.3 percent and 2.9 ± 0.3 percent, respectively, in the groups that received 5 and 10 mg of alendronate per day ($P < 0.001$) and decreased by 0.4 ± 0.3 percent in the placebo group. The femoral-neck bone density increased by 1.2 ± 0.4 percent and 1.0 ± 0.4 percent in the respective alendronate groups ($P < 0.01$) and decreased by 1.2 ± 0.4 percent in the placebo group ($P < 0.01$). The bone density of the trochanter and total body also increased significantly in the patients treated with alendronate. There were proportionally fewer new vertebral fractures in the alendronate groups (overall incidence, 2.3 percent) than in the placebo group (3.7 percent) (relative risk, 0.6; 95 percent confidence interval, 0.1 to 4.4). Markers of bone turnover decreased significantly in the alendronate groups ($P < 0.001$). There were no differences in serious adverse effects among the three groups, but there was a small increase in nonserious upper gastrointestinal effects in the group receiving 10 mg of alendronate. **Conclusions.** Alendronate increases bone density in patients receiving glucocorticoid therapy. (N Engl J Med 1998;339:292–9).

Glucocorticoid induced bone loss is now a well recognised clinical problem.¹ It may lead to osteoporotic fractures² and occurs in patients being treated with glucocorticoids for different conditions such as rheumatoid arthritis,³ asthma,⁴ and polymyalgia rheumatica.⁵ Rapid bone loss may occur during the first year of treatment⁶ and there is justified concern about the need for preventative strategies for patients starting on glucocorticoid treatment so that osteoporosis does not occur. However, the increased awareness of the need to diagnose and prevent osteoporosis in general,^{7,8} the complex pathogenesis of steroid induced bone loss,⁹ the limited evidence to support current strategies for the prevention of steroid bone loss,^{10,11} and the pharmaceutical zeal to produce new agents and new applications of present ones^{12,13} has led to a confused atmosphere for the practising clinician treating patients

on glucocorticoids. There is a wide variety of advice available^{10,12,14–19} but uncertainty remains about the precise way forward.^{20–22}

Osteoporosis is defined as a progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.⁷ In the UK osteoporosis results in over 200 000 fractures each year, at an annual cost to the National Health Service of over £940 million, and more than one third of adult women will sustain one or more osteoporotic fractures in their lifetime.⁷ Strategies for the prevention and identification of risk factors for osteoporosis are therefore important so that the burden of osteoporotic fractures can be reduced. Much attention has focused on risk factor frequency so that subjects at high risk of osteoporosis can be targeted for

bone mass measurements and preventive treatment. The use of risk factor questionnaires has been limited in their success in identifying patients likely to develop fractures. However, it is now recognised that certain risk factors are more useful predictors of fracture than others.²³ These are reduced bone mineral density, history of a prior fracture after the age of 40 years, history of a fracture at the hip, wrist or vertebra in a first degree relative (family history), being in the lowest quartile in weight (≤ 57.8 kg, thinness), and current cigarette smoking. Bone mass is accurately assessed by measurements of bone mineral density. A working group of the World Health Organisation has defined osteoporosis as a bone mineral density that is 2.5 SD below the mean peak value in young adults.²⁴ This is known as the T score. Lesser degrees of bone loss are defined as osteopenia (T score between 2.5 SD and 1 SD below the mean peak value in young adults). These limits are useful in making a diagnosis and also in assessing which patients are at risk.²⁵ Bone density is widely measured by dual energy x ray absorptiometry (DXA)²⁶ of the lumbar spine (particularly trabecular bone) and of the femoral neck (predominantly cortical bone). However, other methods involving assessment of the appendicular skeleton (peripheral DXA (pDXA) and ultrasound measurements of the calcaneus) are being developed for use in clinics and health centres.²⁶

Bone remodelling is a complex process involving a number of cellular functions directed towards the coordinated resorption and formation of new bone. A sequence of events is initiated by local events so that osteoclastic activity produces bone resorption. This is followed by attraction, proliferation, and differentiation of osteoblast cells which lay down new bone and repair the resorption defects caused by resorbing osteoclasts.^{27,28} The end point of bone remodelling is the maintenance of the bone mass. It is governed by systemic hormones and local factors including glucocorticoid and sex steroids. Bone loss may occur if the bone resorbed is not fully replaced due to overactivity of the osteoclast or underactivity of the osteoblast. The functions of osteoblasts and osteoclasts may be assessed by biochemical bone cell markers such as serum bone specific alkaline phosphatase, osteocalcin, and type I procollagen peptides (bone formation) and serum or urine pyridinoline crosslinks (bone resorption).²⁹

Extent of the problem

It is generally accepted that moderate to high dose glucocorticoid therapy is associated with loss of bone and increased risk of fracture.¹⁵ Some experts believe that at doses of more than 10 mg prednisolone orally per day, all patients lose significant amounts of bone.¹⁷ This is not necessarily so as some Caucasian and Afro-Caribbean patients often seem to be protected from bone loss and osteoporosis, even when receiving high doses of oral glucocorticoids. Also, not all postmenopausal women on chronic steroid and oestrogen treatment are osteoporotic³⁰ and, in some instances, the glucocorticoid induced bone loss is superimposed on bone loss which is already increased because of the underlying disease process. Inflammation in polymyalgia rheumatica increases bone resorption and appears to have a more detrimental effect on bone than the glucocorticoid treatment.³¹ This disorder is associated with high levels of cytokines such as interleukin 6³² which is known to stimulate osteoclast formation and prevents osteoclast apoptosis.³³ Nevertheless, in many patients given high dose corticosteroids

for many years (>10 mg prednisolone per day) bone loss is most rapid soon after starting treatment and occurs to a similar extent from the proximal femur and the lumbar spine.⁶ A recent cross sectional study in general practice in Nottinghamshire was undertaken to determine the prevalence of continuous use of oral steroids in the general population and the extent to which patients taking oral steroids were taking treatment to prevent osteoporosis.³⁴ Three hundred and three patients were currently taking "continuous" oral glucocorticoid treatment, representing 0.5% of the total population studied. The usual steroid prescribed was prednisolone (97%) and the mean dose was 8.0 mg/day. Nineteen per cent of the patients were receiving prednisolone for asthma and chronic obstructive airways disease. Only 14% (41) of the overall group of 303 patients had received treatment for the prevention of osteoporosis. It is suggested that there may be at least 250 000 people in the UK taking continuous oral steroids who need prophylaxis against osteoporosis.

However, in respiratory medicine many patients receive inhaled steroids, often with intermittent courses of oral prednisolone. There is concern about the effect of this type of treatment and its potential for putting patients at risk of osteoporosis.³⁵ The evidence from published studies has been confusing, partly because biochemical bone cell markers have been used at the end point as well as bone density. Even though inhaled beclomethasone at a dose of 2000 μ g/day produces a significant decline in serum osteocalcin after nine weeks of treatment,³⁶ and there is a decline in bone density in patients taking inhaled steroids only at more usual lower doses,³⁷ there is little evidence that long term treatment with inhaled steroids is associated with an increased risk of osteoporotic fractures.³⁸⁻⁴⁰ It seems that it is a high daily dose of inhaled steroids, rather than the duration of the dose, that may adversely affect bone density. A comparison of the effect of fluticasone and budesonide on bone markers and bone density during one year of treatment did not show a decrease in bone density.⁴¹

Glucocorticoids produce bone loss by means of direct and indirect effects on bone.¹⁷ Histomorphometric studies⁴² indicate that glucocorticoids depress osteoblast function. In patients treated with glucocorticoids there is a greater than normal deficit in the quantity of bone replaced in each remodelling cycle. This leads to an enhanced rate of bone loss, which is more severe in parts of the skeleton with a high proportion of cancellous bone such as the vertebrae and ribs, where fractures frequently occur. The low osteoblast activity is confirmed by reduced osteocalcin levels in glucocorticoid dependent asthmatic patients.⁴³ The possible reversibility of the effects of glucocorticoids on the osteoblast is important from the clinical point of view. There is evidence from patients treated for Cushing's syndrome that the deleterious effects of glucocorticoids on the skeleton are reversible.^{44,45} However, in practice if loss of trabecular plates and microfractures has occurred within the bone, it is unlikely that a significant reversal of the effect can be expected on withdrawal of glucocorticoid treatment.

In addition, there are important indirect effects of glucocorticoids on bone.¹⁷ These include a generalised defect in calcium transport, secondary hyperparathyroidism, and deficiency of anabolic hormones (table 1). As a result there is impaired gastrointestinal absorption of calcium, hypercalciuria, secondary hyperparathyroidism, deficiency of oestrogen and testosterone, as well as the direct effects on bone turnover.

Table 1 Effect of glucocorticoids on bone (after Lukert¹⁷)

Direct	Indirect (systemic)
Decrease in osteoblast function	Defects in calcium transport: gastrointestinal, renal, parathyroid
Inhibition of gene expression for type I collagen	Secondary hyperparathyroidism
Decrease in bone matrix proteins	Diminished secretion of gonadal hormones: gonadotrophins, oestrogen, testosterone
Increased bone resorption	Decreased adrenal secretion of oestradiol, androstenedione Decreased response to human growth hormone

Prevention by bisphosphonates

PAPER BY SAAG *ET AL*¹³

In order to prevent the skeletal side effects of glucocorticoid treatment there is much interest in developing strategies for use in clinical practice. The bisphosphonate drugs have been widely used as agents to prevent bone resorption⁴⁶ and the paper by Saag and colleagues¹³ for the Glucocorticoid Induced Osteoporosis Interventional Study Group reports the results of a randomised placebo controlled study of the amino bisphosphonate alendronate in 477 patients who were receiving glucocorticoid therapy. The patients studied were men and women of a wide age range (18–83 years) who were receiving their treatment for a variety of different disorders of which only up to 10% were for respiratory disorders. The multicentre study was conducted in two parts in parallel, one involving 232 patients at 15 centres in the USA and the other involving 328 patients at 22 centres in 15 other countries. The patients enrolled were receiving at least 7.5 mg prednisolone or equivalent for different lengths of time (<4 months to >12 months) and were included in the study irrespective of baseline bone mineral density. The patients were randomly assigned to receive placebo or 5 mg or 10 mg alendronate. The treatment lasted for less than a year (48 weeks) and all patients received calcium and vitamin D supplements daily. There were a significant number of exclusion criteria but, of the 232 postmenopausal women included (49%), 34% were taking oestrogen replacement. One hundred and forty one men (29.5%) were included in the study. The biochemical bone markers measured at the beginning of the study were within the reference range. In particular, the bone alkaline phosphatase (bALP) was not reduced as might be expected in response to glucocorticoid treatment. Unfortunately this study was not statistically powered to show the effect of alendronate on prevention of fractures.

This paper describes an international collaboration to study the use of alendronate for the prevention and treatment of glucocorticoid induced osteoporosis. Alendronate is known to be a very effective agent for the prevention⁴⁷ and treatment of osteoporotic fractures^{48,49} so studies of the use of alendronate in glucocorticoid bone loss have therefore been eagerly awaited. There was an increase in mean lumbar spine bone density of 2.1% and 2.9% in response to doses of 5 mg and 10 mg alendronate, respectively ($p < 0.001$). The corresponding values for the placebo group showed a decrease of 0.4%. The increases in the femoral neck bone density were less remarkable and the biochemical

bone marker responses decreased significantly in the alendronate treated patients ($p < 0.001$).

In postmenopausal women under 60 years of age 5 mg of alendronate given daily in order to prevent bone loss produced an increase in bone density at the lumbar spine of 2.7%.⁴⁷ These patients were not receiving hormone replacement therapy and the majority did not have bone mineral density results in the osteoporotic range. Saag *et al* reported that 5 mg alendronate given to postmenopausal women on glucocorticoid treatment who were receiving oestrogen replacement produced a 1.6% increase in lumbar spine density with similar results (1.5% increase) following 10 mg alendronate. However, in the patients not receiving oestrogen the postmenopausal women responded by an increase of 4% following 10 mg alendronate. This suggests that women not on oestrogen replacement but receiving glucocorticoid therapy may respond more to alendronate when lumbar spine bone density is used as the outcome parameter.

The duration of glucocorticoid therapy did not have any effect on the response to treatment, nor apparently did the underlying disease state. However, there is concern about the minimal loss of lumbar spine bone mass in the patients in the placebo group, as would be expected in response to glucocorticoids. This suggests that the effect of alendronate in preventing bone loss may not have been very robustly tested in some patients. In the subgroup of patients with bullous skin diseases who were receiving high daily doses of glucocorticoids (mean dose 23.5 mg prednisolone or equivalent) lumbar spine bone density in the patients in the placebo group decreased by 3% while in those treated with alendronate it increased by 2% from baseline, giving a total difference of 5%. Biochemical bone markers of bone turnover, bone formation, and bone resorption are known to decrease in response to alendronate treatment in postmenopausal women.^{50,51} Also, bone turnover is increased in postmenopausal patients with osteoporosis.⁵² The effect of glucocorticoids on bone suppresses bone turnover,¹⁰ especially by suppressing osteoblast activity. Approximately 50% of the patients treated with alendronate in the study by Saag *et al* underwent bone marker measurements. The type of patients (sex and postmenopausal status) is not revealed. However, the response curves are related to reference values for premenopausal women. There is evidence of increased bone resorption (urinary N telopeptides of type I collagen) at baseline and in the placebo group. However, the bone formation marker (serum bone specific alkaline phosphatase) is within the reference range at baseline and was not suppressed, as might have been expected. In addition, the placebo values throughout the study did not decrease in response to glucocorticoid therapy. Serum osteocalcin (another bone formation marker used as an indicator of osteoblast activity) is known to decrease in concentration following beclomethasone treatment in postmenopausal asthmatic women.³⁶ It is possible that, although bone specific alkaline phosphatase and osteocalcin are both osteoblast markers, they may represent markers of different stages of osteoblast function⁵³ and therefore respond to specific actions of glucocorticoids on the osteoblast.

PREVIOUS BISPHOSPHONATE STUDIES

Intermittent treatment with etidronate has been shown to prevent corticosteroid induced bone loss in the lumbar spine.^{54–56} No change in bone density occurred compared with placebo in the femoral neck and, when

patients were treated with etidronate, bone loss at the lumbar spine was prevented.^{54,56} Previous information on the use of alendronate in glucocorticoid treated patients is very limited. In patients with sarcoidosis 5 mg alendronate prevented radial bone loss of 4.5% in 12 months.⁵⁷ The improvement in bone density documented in these studies occurred within one year of treatment and it is possible that these changes may be related to bone remodelling transient.⁵⁸ It is therefore important that much longer studies assessing the effect of bisphosphonates on glucocorticoid bone loss are undertaken.

The structure–activity relationships of bisphosphonates and the subtle differences between the molecular mechanisms of action of etidronate and alendronate may be of interest when assessing the use of the drugs in preventing glucocorticoid induced bone loss. In vitro studies have shown alendronate to be significantly more potent than etidronate⁴⁶ and, in postmenopausal osteoporosis, alendronate produces a greater increase in lumbar spine bone density than etidronate after three years of treatment.^{48,59} The limited data available on alendronate and etidronate do not show any evidence of difference in potency between these bisphosphonates when used to treat glucocorticoid induced bone loss. Bisphosphonates are pyrophosphate analogues with a strong affinity for mineralised tissues and are potent inhibitors of bone resorption.⁴⁶ These compounds have a P–C–P backbone structure. The phosphorus atoms are linked to a geminal carbon having sites for two other groups (described as R₁ and R₂) which have enabled development of different analogues with different anti-bone resorptive potencies. The R₁ site is termed the head or hook and is the predominant determinant for hydroxyapatite binding. The R₂ site is termed the bone tail or bioactive moiety and is chemically modified to produce different compounds.⁶⁰ In etidronate the R₂ is a methyl group (CH₃) and in alendronate the R₂ has a three-carbon side chain with a terminal amino group ((CH₂)₃ NH₂).⁶¹ The increased side chain increases lipophilicity which may permit better access to cell compartments. Also, the presence of an amino group in the side chain gives a many hundred times increase in inhibition of bone resorption in potency in vitro.⁶⁰

Bisphosphonates act by inhibiting the activity of the osteoclasts leading to apoptosis. This may be by a direct action on the osteoclast or by stimulating the secretion of an inhibitor of osteoclast recruitment by the osteoblast.⁴⁶ Although the exact molecular targets have not yet been identified, there is some evidence that the amino bisphosphonates (such as alendronate) produce different molecular changes from the non-amino bisphosphonates such as etidronate and clodronate. Clodronate can be metabolised to a cytotoxic, non-hydrolysable analogue of ATP⁶² but the amino bisphosphonates are not metabolised in this way. The amino bisphosphonates cause apoptosis following inhibition of post-translational prenylation of proteins such as Ras, as well as affecting the enzymes of the mevalonate pathway.⁶³ The bisphosphonates can therefore be grouped into those that are metabolised in cells and inhibit cytokine secretion from macrophages (such as etidronate and clodronate) and those that are not metabolised and enhance cytokine production (such as alendronate and pamidronate).⁶⁴ This may be of particular importance in preventing bone loss in patients with inflammatory disease.

Strategy for management

How therefore should we manage our patients who are starting glucocorticoid treatment for respiratory disease? Before we can devise a strategy and consider the need for prophylactic treatment there are many variables that need to be recognised. For instance, is the patient at risk of osteoporosis anyway because, for example, of a family history of hip fracture? Does the patient already have undetected bone loss before the start of glucocorticoid treatment? Is the disease itself likely to cause bone loss because of bone resorption secondary to cytokines? Bone loss may occur very quickly in response to glucocorticoid treatment, or it may not occur at all. At present we do not have the means to detect which response is likely in a patient. Some ethnic groups may be more likely to develop steroid induced osteoporosis than others. If we use the drugs at present licensed for osteoporosis treatment such as hormone replacement or bisphosphonates, how long should the treatment last? Will it give side effects? How should we monitor the

All patients starting oral corticosteroids therapy for 3 months or longer including patients on inhaled steroid if at a high dose should:

A. Be advised about lifestyle measures to prevent bone loss.

B. Have a bone density measurement of the lumbar spine and femoral neck at the beginning of treatment.

C. Be assessed for risk factors for osteoporosis (questionnaire) and have simple pathology tests to detect pre-existing risk factors for osteoporosis (LFTs, creatinine and electrolytes, bone profile, TSH, FBC and ESR testosterone (in men)).

A. Important life style measures to aid prevention of osteoporosis:

1. Maintain adequate dietary calcium and vitamin D intake (1500 mg calcium and 400 IU vitamin D per day).
2. Moderate alcohol intake.
3. Reduce cigarette smoking.
4. Daily weight bearing exercise.
5. Take lowest dose of glucocorticoid

B. If BMD reduced:

osteopenia (T –1 to –2.5)
osteoporosis (T < –2.5)
Start treatment
HRT
Bisphosphonates
Vitamin D and calcium
Repeat BMD in 2 years

If BMD normal:

Treat risk factors if possible
Ensure adequate calcium and vitamin D intake
Plan repeat BMD for 1 year

C. Risk factor assessment:

No. of cigarettes smoked per day.
Have you had a fracture if over 40 years of age?
Did one of your parents have a fracture?
Measurement of height and weight → BMI.
Dietary calcium intake.
Age.
Menopausal status.
BMD result.

Box 1 Suggested working schme for patients with respiratory disease starting glucocorticoid treatment. LFT=liver function test; TSH=thyroid stimulating hormone; FBC=full blood count; ESR=erythrocyte sedimentation rate; BMD=bone mineral density; HRT=hormone replacement therapy.

LEARNING POINTS

- * Bone loss leading to osteoporotic fractures is a significant consequence of glucocorticoid treatment of respiratory disease.
- * Bone loss occurs primarily in patients receiving oral glucocorticoids which directly suppress osteoblast function.
- * Not all patients receiving glucocorticoid treatment develop bone loss.
- * Before the start of glucocorticoid treatment patients should be assessed for potential bone loss by bone densitometry and risk factor assessment.
- * Bone loss can be prevented and treated by life style measures, hormone replacement, bisphosphonates, or vitamin D and calcium.

effect of treatment and is the cost justified? Are there other steroid like drugs that can be used that are bone sparing? Long term evidence for the prevention of glucocorticoid bone loss is not available and therefore a well founded strategy is difficult to formulate. A simple working scheme is proposed in box 1.

Eastell and colleagues¹⁰ have produced a very comprehensive review of the management of glucocorticoid induced osteoporosis. In particular, it provides well documented references to trials of the bisphosphonates and other agents for the prevention of steroid induced bone loss. However, it may not be necessary for all patients starting on oral glucocorticoid treatment for six months or more to have preventative therapy. More information is required about the dose of oral corticosteroid that causes bone loss. There is also some evidence that vertebral fractures may occur at a lower bone density in glucocorticoid treated patients than in those with other types of bone loss.⁶⁵

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