# New perspectives in the prevention and treatment of glucocorticoid-induced osteoporosis

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**ABSTRACT**

*Glucocorticoid-induced osteoporosis represents an important proportion of the so-called secondary osteoporoses. The pathogenetic bases of this disorder have been uncovered, making possible a rational approach to the prevention and therapy of bone complications in various types of patients undergoing corticoid treatment. Apart from the universally accepted inverventions (i.e., calcium, vitamin D, bisphosphonates, etc.), a number of new, potentially useful drugs are under investigation.*

*In this chapter we will review our accumulated knowledge of these compounds, which should certainly contribute to enlarge the armamentarium of the physician who is going to treat patients with glucocorticoids.*

**Introduction**

Glucocorticoids (GC) were introduced into clinical practice nearly 50 years ago and have become pivotal to the management of a large number of conditions. Their therapeutic potential is limited to some extent by their high incidence of side effects. With chronic use, one of the principal complications is the development of osteoporosis (1, 2), which was described within a few years after the introduction of these drugs to clinical practice in the 1950s. It should be emphasized, however, that this is only a problem with chronic steroid use. The use of these drugs, even in high doses, over a period of days to weeks will seldom result in clinically significant changes, and any bone loss produced is likely to be reversible as the patient returns to good health.

Because of the widespread distribution of the GC receptor, these agents are able to impact on bone and calcium metabolism. The most consistently demonstrated effects of GC on bone are on the osteoblast, whether *in vivo* or *in vitro*. Animal and human studies of bone histomorphometry demonstrate impaired bone formation. Both the rate of bone production within each bone modelling unit and the duration of activity of each unit are reduced. The effects of GC on osteoclasts are contradictory. There is evidence that GC increase osteoclastogenesis in bone marrow but also that they lead to apoptosis of mature osteoclasts. These opposing effects may account for the findings in organ culture that GC can either increase or decrease bone resorption, depending on the culture conditions. In organ culture, GC effects may be contributed to by their inhibition of production of local osteolytic cytokines such as interleukins-1 and -6, the tumour necrosis factors, and leukaemia inhibitory factor, and their stimulation of macrophage-colony stimulating factor production by osteoblasts.

Studies have consistently demonstrated an inhibition of calcium absorption associated with GC 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 GC treatment there is a substantial rise in urine calcium excretion, which is not accounted for by changes in the serum ionized calcium or the glomerular filtration rate. This suggests that GC directly regulate tubular resorption of calcium. There is also evidence for malabsorption of phosphate in both the gut and renal tubule to be associated with GC use.

Sex hormones are important regulators of bone metabolism, and hypogonadism in either sex is associated with the development of osteoporosis. GC acutely depress plasma levels of testosterone in men and their chronic use is associated with a dose-dependent reduction in free testosterone concentrations of approximately 50%. These changes appear to result from inhibition of gonadotropin secretion and a reduction in the number of gonadotropin-binding sites in the testis. High-dose GC therapy is associated

with oligomenorrhoea in women, suggesting a similar effect on the pituitary-gonadal axis.

Bone loss is evident within months of the start of steroid therapy. Bone density in steroid-treated subjects studied cross-sectionally is related both to the duration of steroid treatment and to the average dose of these drugs. It is also dependent on the factors that influence the patient's pre-treatment density, such as sex, body weight and age. The condition for which glucocorticoids are prescribed may also contribute to bone loss. Many chronic inflammatory conditions themselves are associated with bone loss, possibly because cytokine release stimulates osteoclast activity (3).

Cross-sectional studies of patients treated for periods of 5 years show that the integral bone mineral density (BMD) of the lumbar spine and proximal femur is about 20% below control values. The more rapid loss in the vertebrae is probably a reflection of the greater surface-to-volume ratio of trabecular bone. Since bone remodelling takes place only at the bone surfaces, this bone type responds more rapidly to any change in the bone balance. This pattern of bone loss results in fractures predominantly in trabecular bone, particularly the vertebrae and ribs.

The purpose of this article is to review current therapies and possible future approaches to the prevention and treatment of GC-induced osteoporosis.

**Identification of subjects at risk**

Most individuals using glucocorticoid drugs in doses greater than the equivalent of prednisone 5 mg/day will experience bone loss and may be at risk of fractures. In order to evaluate the risk of fractures, bone density must be measured. Since vertebral bodies are a common site of bone loss and fracture, they are the logical place at which to measure bone density. 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 most trabecular-rich part of the proximal femur and generally shows the most marked reduction in steroid-treated patients.

The development of biochemical markers of bone turnover has been substantially driven by the hope that these would be useful in assessing an individual's fracture risk. There is little convincing evidence that this is so in steroid-treated subjects, although the available data is very limited.

**Prevention and treatment**

Since the major outcome of osteoporosis is the occurrence of a fracture, management can be divided into 3 phases. Primary prevention is indicated for those patients with a normal bone mass who are exposed to the risk of bone loss such as occurs with the onset of menopause or the introduction of corticosteroids. Secondary prevention is appropriate for those who have lost substantial bone but who have not yet sustained a low-trauma fracture. Active treatment is required for those who have already experienced a fracture and who need both symptom control and measures to prevent further fractures.

Since osteoporosis results in an increased risk of low-trauma fractures, any treatment aimed at preventing such fractures is in fact a measure of primary prevention. In established osteoporosis, where fractures have already occurred, treatment is first required to alleviate the symptoms and then should be directed to avoid further fractures. The options available for the alleviation of symptoms due to fracture consists of surgical or physical measures in addition to analgesia. Although secondary prevention and treatment have many elements in common, there are important differences in their management. The most important is that in established osteoporosis the need for treatment is urgent due to the fact that every additional fracture multiplies the risk of future events, thus justifying long-term and relatively costly treatment.

In the individual patient, the results of these efforts can be monitored through an increase in BMD, but in order to justify treatment it has to be shown that it also decreases the fracture incidence. Such evidence can only be provided by large clinical trials performed over at least 3 years, but not all drugs have been tested in this way. Although some drugs increase BMD to such an extent that an effect on the fracture incidence seems likely, this is only an assumption, and requires proof from an appropriately designed clinical trial. This is particularly important when drugs with different compositions are compared, because a gain in BMD does not necessarily correspond to an increase in mechanical resistance. For instance, fluoride increases trabecular BMD more than bisphosphonates, but its anti-fracture efficacy is lower. On the other hand, the reduction in fracture incidence may be greater than that predicted by the increment in BMD, as has been seen in studies of alendronate and salmon calcitonin.

**Indications**

Establishment of the level of bone density at which intervention is 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 postmenopausal osteoporosis, i.e. to offer treatment to those whose BMD is more than 1-2 standard deviations below the young normal mean value. It can be predicted that in an individual beginning steroid therapy the BMD will drop a further 1-2 standard deviations below its current level during the first year of treatment, and this should be kept in mind in the decision-making process. A past history of fracture after minimal trauma is also a good reason for weighting the balance in favour of intervention, since it implies that the individual skeleton is already only marginally adequate to withstand the trauma of daily living.

**Effective available pharmacological therapies**

The general measures that would be considered in osteoporotic patients (mobilization, attention to nutrition, cessation of smoking, moderation of alcohol intake) are also appropriate in those receiving steroids, whatever their bone density. In those patients with low bone density as defined above, pharmacological intervention is usually also necessary.

The optimisation 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 (4-13). Since the therapeutic efficacy of these agents is comparable, the final choice will be based on a consideration of the patient's other medical problems, possible side effects, and cost. In a patient with marked bone loss, more than one of these agents could be prescribed, together with other agents such as fluoride (14-23). The use of such combination regimens results in substantial increases in bone density (24, 25).

The availability of effective interventions in this condition places a responsibility on any clinician prescribing GCs to assess the fracture risk and to provide prophylaxis against bone loss. The widespread adoption of this strategy will result in far fewer patients on GC having to accept the morbidity of multiple fractures in addition to that of their other medical conditions.

**Other pharmacological interventions**

*Thiazides*

Thiazide diuretics have been advocated as a therapy for both postmenopausal and GC-induced osteoporosis (26, 27). They clearly diminish urinary calcium loss in steroid-treated subjects and the addition of a thiazide to alphacalcidol and calcium leads to significantly more positive changes in bone mass in steroid-treated subjects. However, studies demonstrating a beneficial effect on bone density are limited and thiazides frequently cause hypokalaemia in steroid-treated subjects, which means that their use requires close supervision, and sometimes the addition of a potassium supplement.

*Anabolic steroids*

Anabolic steroids such as stanozolol (5 mg daily by mouth) and nandrolone (50 mg IM every 3 weeks) increase bone mass in women with established osteoporosis by 5-10% (28). These increases are modest and may be due to a decrease in bone resorption, rather than to an increase in new bone formation. In women anabolic steroids are associated with fluid retention and androgenic side effects such as acne, weight gain and hirsuitism. Prolonged administration may lead to abnormal liver function tests and even hepatocellular tumours.

*Testosterone*

Testosterone replacement in hypogonadal men with osteoporosis increases spine bone density by up to 15%, particularly if the epiphyses are still open (29). Treatment may also increase muscle mass and improve well being. Osteoporotic men with evidence of hypogonadism should therefore be offered testosterone replacement therapy after discussion of the potential risks and benefits. Side effects of testosterone treatment include increased libido, mild truncal acne, weight gain, a rise in the haematocrit, and azospermia in 50-70% of cases. Although it has been suggested that testosterone treatment has an adverse effect on glucose tolerance and serum lipids, the overall impact on cardiovascular disease (CVD) risk factors is probably neutral.

The long-term risk of testosterone treatment in prostatic disease remains uncertain. The dose and frequency of administration are adjusted after a few months of treatment based on the patient's tolerance and serum testosterone, SHBG and gonadotrophin measurements. The safety of the treatment is also checked by monitoring the patient's full blood count, biochemical profile, glucose, serum lipids and prostate-specific antigen.

Preliminary studies suggest that testosterone supplementation also increases spine bone density by 5% in eugonadal men with osteoporosis, but there is currently no data to show whether this is associated with a reduction in fracture risk. Further studies will be required to evaluate the safety and efficacy of testosterone supplementation in eugonadal men.

*Selective oestrogen receptor modulators*

The selective oestrogen receptor modulators (SERMS) form a group of 'designer oestrogens' with selective tissue-specific effects on the oestrogen receptors. These tissue-specific oestrogens were designed to preserve the beneficial effects of oestrogen, including protection against osteoporosis and CVD, but also to have no undesired effects on the reproductive organs (endometrium and breast).

Tamoxifen was the first of this class of drugs to be clinically evaluated. Because of its anti-oestrogenic effect on the breast, tamoxifen is used to prevent recurrences in breast cancer patients. Tamoxifen was later found to have an oestrogenic effect on the cardiovascular and skeletals systems, but unfortunately it was also found to increase the incidence of endometrial cancer (30-32).

Raloxifene was initially shown in animal models to act as an oestrogen receptor antagonist in the breast and endometrium, but as an oestrogen agonist in the skeletal and cardiovascular systems. In a recent large, randomized study of healthy, recently postmenopausal women, raloxifene 60 mg/day was shown to be the lowest dose with significant and clinically relevant effects on bone turnover and bone mass (33). This is now the recommended dose for osteoporosis, since it reduces bone turnover by 25-40%, increases BMD at the spine, hip and total body by 1.2% to 1.6% without stimulating uterine or breast tissue, and is generally well tolerated. A large study of raloxifene in elderly women with low bone mass and/or a prevalent vertebral fracture have revealed a similar effect on bone turnover and bone mass to that in younger women and a 30-50% reduction in the incidence of low-trauma vertebral fracture (34).

Raloxifene significantly reduces aortic atherosclerosis in cholesterol-fed rabbits, and in early and late postmenopausal women it decreases serum total cholesterol, LDL-cholesterol, and lipoprotein a, and increases $HDL_2$-cholesterol, but to a lesser extent than hormone replacement therapy (HRT) (35, 36). Further clinical trials will be necessary to determine whether these favourable biochemical effects are associated with protection against CVD. Because of its anti-oestrogenic effect, raloxifene would be expected to be associated with an increased incidence of hot flushes; but at doses of 60-120 mg/day it does not seem to substantially increase the frequency of such menopausal symptoms. Furthermore, since hot flushes tend to decrease with time, this does not seem to result in the discontinuation of raloxifene treatment.

*Strontium*
In preliminary studies, strontium has been shown to increase lumbar spine BMD in postmenopausal women by about 3% per year and to decrease vertebral deformities. The effect on BMD must be interpreted with caution, however, since the bone content of strontium alters densitometric values. Strontium preparations are not currently available for clinical use.

*Growth factors*
Growth hormone has not yet been shown to be effective in the treatment of osteoporosis, although it has a positive effect on bone metabolism and increases BMD in patients with growth hormone deficiency. Insulin-like growth factor (IGF) has also been tested and some positive effects have been demonstrated in the elderly, but the clinical development of these peptides will remain limited as long as they have to be administered parenterally.

**Nutritional measures**
Although nutrition influences bone mass by only a few percentage points, it has a definite place in the general management of osteoporosis. Calcium and vitamin D are of course the most important nutrients, but new information on proteins and salt intake need to be incorporated into the current management of GC-induced osteoporosis.

*Protein*
Adequate protein intake lowers bone loss, while an insufficient intake is a pathogenetic factor for osteoporosis at all ages (37,40). Protein deficiency increases the risk of hip fracture by decreasing muscle strength and increasing the risk of falls, as well as through an effect on femoral neck BMD. It also adversely influences the clinical outcome of elderly patients with hip fractures, and, although rarely diagnosed, is characteristic of the ailing elderly patient with osteoporosis.
An intake of 0.8 g per kg body weight is considered to be adequate for adults of all ages. Although protein requirements seem to decline with age, they often remain unmet. Protein and calcium supplementation accelerates the recovery of elderly patients with hip fractures and decreases their mortality. Supplementation with protein alone leads to an increase of BMD at the hip in elderly patients with osteoporosis. This positive effect should not be confused with the adverse effects of a diet high in animal proteins which, because of its acid load buffered by bone, leads to a negative bone calcium balance and increased urinary calcium excretion. Soya proteins do not have this disadvantage.

*Salt*
A high intake of salt should also be avoided, since it increases urinary calcium excretion and enhances the development of osteoporosis (41,42). The chronic use of thiazides, which lowers urinary sodium and calcium excretion, is associated with a decreased incidence of hip fractures. For these reasons a low salt diet or a thiazide diuretic might reasonably be included as an adjuvant treatment in those patients who are also hypertensive.

*Vitamin K*
Vitamin K is a co-factor for the gamma-carboxylation and activation of osteocalcin. It has been found to be relatively deficient in osteoporotic patients, but although supplementation with vitamin K increases plasma levels of osteocalcin, its effect on BMD is uncertain.

*Fibre*
There is no need to avoid nutrients rich in oxalate or fibre because of their reported inhibitory effect on calcium absorption. Oxalate is rarely consumed in amounts that could have any effect on calcium homeostasis, and the well-established positive role of fibre in preventing constipation and colon cancer outweighs its hypothetical effect on calcium absorption.

*Calcium*
Calcium supplementation, particularly in the elderly, is an important adjuvant to the treatment of GC-induced osteoporosis (43,45). It offsets any tendency to hypocalcaemia and secondary hyperparathyroidism that might occur with the use of inhibitors of bone resorption. The addition of 1 g of calcium above the normal intake reduces the bone loss and fracture rate, but it remains uncertain how far dietary sources can cover this need. The National Institutes of Health (Bethesda, USA) recommend a dietary intake of 1.5 g for men below 65 years, 1 g for postmenopausal women on HRT (1.5 g when not on HRT), and 1.5 g for both sexes over the age of 65 years. These levels are quite high, and difficult to meet on a daily basis. Calcium from man's main nutritional source – dairy products – is as well absorbed as the calcium from commercial supplements. Absorption is about 20% in postmenopausal women when the intake is 1 g and about 30% when the intake is 0.5 g. The amount of low-fat dairy products that provides 1000 - 1500 mg calcium contains only about 100 mg cholesterol, a third of the total permissible intake; and this does not increase plasma cholesterol. Other calcium-rich nutrients, such as nuts, vegetables, and sardines, are rarely taken in amounts large enough to provide 1000 mg, but calcium-rich mineral water may also contribute to the total intake.

*Vitamin D*
Only those patients spending at least 30 minutes per day outdoors may produce enough vitamin D to maintain calcium homeostasis. If the plasma level of 25-(OH)vitamin D falls below 10 nmol/l, the PTH rises above the upper limit of normal and increases bone turnover and loss. Nutritional sources of vitamin D, mainly oily fish, are insufficient to compensate for the lack of UV exposure, and vitamin D supplementation rather than a change in diet is indicated in the management of osteoporosis.

**Physical exercise and therapy**
Intense physical exercise increases BMD in the loaded bone in both young and postmenopausal women, at least transiently, but controlled studies in osteoporotic patients are lacking. In the prevention of vertebral fractures, extension exercises of the back are more effective than flexion exercises (46). Physiotherapy in established osteoporosis allows mobilization of the fracture patient and also increases stability and mobility, which may prevent falls. In symptomatic patients, it not only improves balance and strength and decreases pain and the

need for analgesics, but also improves the level of daily functioning and the quality of life beyond the training period.

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