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# Deflazacort and bone mass

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**Key words:** Deflazacort, glucocorticoid osteoporosis, bone mass, bone densitometry, bone histomorphometry.

## ABSTRACT

*Deflazacort is an oxazoline derivative of prednisolone with anti-inflammatory and immunosuppressive activity which is approximately 25% less potent than prednisone in terms of absolute dosage. Histomorphometry and densitometry techniques have shown that, when used at doses with approximately equivalent anti-inflammatory efficacy, it appears to have fewer detrimental effects on bone mass than prednisone. However, these claims have been questioned on the basis of some doubts regarding the dose equivalence of deflazacort and the glucocorticoid of reference, prednisolone. At present much of the data on bone-sparing effects come from trials that are relatively small or of short duration, even if their number and the consistency of their findings seem reliable. Therefore, well-designed clinical trials are needed, especially to clarify the appropriate ratio of doses for bio-equivalence with prednisone.*

## Introduction

Deflazacort is an oxazoline derivative of prednisolone with anti-inflammatory and immunosuppressive activity. Following clinical trials over more than 20 years, it has been approved in many countries (Italy, France, UK, Germany, Spain) for use in inflammatory diseases. With regard to its effect, it has been claimed to have, at doses with equivalent anti-inflammatory efficacy to prednisolone, less severe adverse effects on bone, carbohydrate metabolism and linear growth. However, these claims have been questioned on the basis of some doubts as to the dose equivalence of deflazacort and the glucocorticoid of reference, prednisolone. The aim of this review is to summarise the available data on the effects of deflazacort on bone mass.

## Assessment of bone mass

With the availability of sophisticated techniques to assess bone mass and remodelling (assays of biochemical markers of bone turnover, radiological and

scintigraphic evaluations, bone densitometry, histomorphometry of bone biopsies) the clinician is faced with difficult decisions regarding the interpretation of the results of these tests.

Among these techniques, quantitative histological measurement (histomorphometry) of iliac crest bone biopsies is a very reliable tool, which has been used to gain a better understanding of the pathogenesis of glucocorticoid osteoporosis, to reveal occult osteomalacia and to monitor the skeletal status of individual patients. Very recently a simple method enabling the two-dimensional imaging of cancellous bone to be viewed within its three-dimensional context has been developed. It complements established bone histomorphometry procedures and has been shown to be a good mass-independent predictor of fracture predisposition in a group of women with and without vertebral compression fractures, but with a similar BMD (Bone Mineral Density) (1). However, bone biopsy is an invasive, painful procedure not easily accepted by patients.

Therefore, in recent years almost all studies on bone mass in steroid osteoporosis have been performed using bone densitometry, which is easier to perform, allows multiple measurements and is well accepted by patients. However, the BMD used routinely for the diagnosis of osteoporosis is a measurement of bone mineral mass (cortical and trabecular) partly normalised by bone area, not a true bone density (the density of mass per unit volume of bone), and has some limitations, especially in predicting trabecular bone volume changes in the short term. For instance, Cosman *et al.* (2) found in a large group of 81 patients with various metabolic bone diseases that the relationships between bone densities in the axial and peripheral regions and histomorphometric variables in the iliac crest are not constant. Moreover, cancellous bone volume and the trabecular structural indices correlated with non-invasive axial BMD measurements only in a heterogeneous group with a large variance in both

parameters, not in the more homogeneous group with osteoporosis.

On the other hand, it is well known that the mechanical strength of bone is not solely a function of its mass or bone mineral density (BMD), but also of the complex architecture of trabecular bone. Unfortunately, microarchitectural changes in bone quality cannot be detected by BMD; therefore it has been suggested that changes in the numerical value for BMD may not have the same structural significance in metabolic bone diseases such as glucocorticoid osteoporosis as in a normal population (3).

### Glucocorticoid and bone

Understanding the actions of deflazacort on bone mass demands knowledge of the adverse effects of supraphysiological doses of glucocorticoids on bone, i.e. of the pathogenetic mechanisms of glucocorticoid-induced osteoporosis. In this bone disease, both cortical and cancellous bone are lost but the latter is more severely affected. The main histologic feature in glucocorticoid-induced osteoporosis is a reduced bone formation rate, represented by decreased wall thickness of the trabeculae, suggesting a decreased activity of osteoblasts. The rate of bone loss is biphasic, with a rapid initial phase during the first 3-6 months which slows down sharply thereafter. We have demonstrated this in the only long-term longitudinal histomorphometric studies of trabecular bone volume changes during glucocorticoid treatment so far reported in the literature (4-6).

The mechanisms proposed to explain the loss of bone that ensues with glucocorticoid excess include decreased osteoblast proliferation and biosynthetic activity, increased bone resorption, hyperparathyroidism resulting from decreased intestinal calcium absorption, and hypercalciuria due to defective vitamin D metabolism. However, the evidence in support of most of these mechanisms are conflicting. Indeed, while earlier histologic studies showed increased eroded surfaces (7, 8), in more recent studies such as our longitudinal histomorphometric study (5), total resorption surfaces were decreased, although not significantly. Likewise, elevated levels of parathormone (PTH), reported in the past as be-

ing due to the malabsorption of calcium found in steroid-treated patients (9), have not been confirmed by more recent studies showing reduced levels of PTH (10, 11). On the other hand, the contribution of changes in vitamin D metabolism to the development of steroid osteoporosis seems to be negligible (12). Moreover, Pearce *et al.* (11) carried out a study in which the rapid bone loss induced by corticosteroid therapy appeared to be due to reduced bone formation, and not to increased bone resorption nor to secondary hyperparathyroidism. In their study the biochemical markers of bone resorption did not change. The initial rapid phase of bone loss with glucocorticoid treatment could be caused in part by an extension of the life span of pre-existing osteoclasts (13) which increases the uncoupling with severely depressed bone formation, as well as by depression of the rate of generation of new BMUs (Basic Multicellular Units).

However, it still seems unclear how an imbalance in the effect exerted by existing BMUs could lead, within 3-6 months, to the rapid bone loss shown by histomorphometric and densitometric methods (5,14,15). Recent studies have found that glucocorticoid excess accelerates the apoptosis (programmed cell death) of osteoblasts and osteocytes (16,17). The premature death of osteoblasts and osteocytes could help to explain the rapid, massive decrease of bone formation found in glucocorticoid-induced osteoporosis. The large number of apoptotic osteocytes adjacent to the subcondral fracture crescent found in whole femoral heads obtained from patients with steroid osteoporosis (17) support this suggestion. Indeed, collapse of the femoral head is far more common in corticosteroid osteoporosis than in postmenopausal osteoporosis, the prevalence of apoptosis being greater in the former (18).

### Deflazacort and bone

The first studies on the tolerability of deflazacort (formerly called oxazacort) suggested a less deleterious effect of this steroid on urinary excretion of calcium than prednisone (19). Subsequently, the observations were extended to a group of 22 normal healthy volunteers, using

approximately equivalent anti-inflammatory doses of prednisone and deflazacort (20). It was concluded that deflazacort influences hydroxyproline and overall calcium urinary excretion to a lesser extent than prednisone, at least on a short-term basis. In a double-blind study of deflazacort and prednisone in 26 patients with chronic inflammatory diseases (especially rheumatoid arthritis and polymyalgia rheumatica), prednisone induced a rapid increase in the level of daily calcium excretion that was not evident with deflazacort (21).

As the negative calcium balance induced by the chronic administration of higher than physiologic doses of glucocorticoid has been claimed to play an important role in the development of osteoporosis (7), the less severe adverse effects on the calcium balance found with deflazacort treatment suggest that the effect of deflazacort on bone mineral metabolism could be less deleterious than that of prednisone. In keeping with this hypothesis, many authors have demonstrated by means of a variety of techniques that the loss of bone mass or density is lower with deflazacort than with prednisone. A preliminary, longitudinal short-term (7 month) histomorphometric study including 21 patients treated with equivalent anti-inflammatory and substitutive activity doses of deflazacort or prednisone showed that the latter produced a higher reduction of trabecular bone, -34.3 % and -13% respectively (14).

The view that deflazacort, although comparable with prednisone in anti-inflammatory activity, is significantly less harmful to cancellous bone than prednisone has been supported by the only prospective, comparative, long-term histomorphometric study available to date (6). Multiple bone biopsies from the iliac crest of 18 pairs of well-matched patients allowed us to describe the time-related trabecular bone loss and to elicit differences between patients treated with prednisone and deflazacort. The kinetics of trabecular bone loss induced by the two corticosteroids, described using a negative exponential function, are similar, with a very rapid rate of loss within the first 3 to 9 months which slows down sharply thereafter (Fig. 1). Particularly relevant is the finding that the bone loss

rate induced by prednisone is significantly higher than that induced by deflazacort. Moreover, the estimated loss rate/year after 3 years of therapy is significantly higher in prednisone-treated patients (-3% versus -1.1%, respectively), suggesting that the less harmful effect to trabecular bone of deflazacort is long lasting.

The studies which have described a bone-sparing effect of deflazacort using absorptiometric techniques are much more numerous. The first, a 12-month study of 22 patients requiring corticosteroid therapy, revealed a 21% per year bone loss during prednisone treatment and only a 10% loss with deflazacort (22). Thereafter, a bone-sparing effect was demonstrated in two randomised double blind prospective trials of deflazacort versus prednisone, in males with newly diagnosed rheumatoid arthritis, and in juvenile chronic arthritis. Indeed, patients receiving deflazacort experienced spinal bone loss at one-third the rate of that observed in the subjects given prednisone at an equivalent dosage (23),

and the children showed better maintenance of their spinal bone mineral content during the first year of deflazacort (24). In the long term, as well, deflazacort appeared to be as effective as prednisone in improving the standard markers of disease activity and to have less severe side effects, especially on bone as demonstrated in a non-blinded randomised trial over 4 years in 72 patients with sarcoidosis (25).

A double-blind study on the long-term effects of deflazacort showed that also with high doses, usually given to patients with nephrotic syndrome, the bone decay rates per month were lower than in the prednisone group, despite a similar therapeutic effect on nephrotic syndrome (26). In another controlled study of 40 patients, deflazacort was more effective than prednisone in limiting relapses in steroid-dependent idiopathic nephrotic syndrome and, overall, induced a less marked decrease in bone mineral content than prednisone (27).

Deflazacort has been extensively studied in kidney transplant patients, who

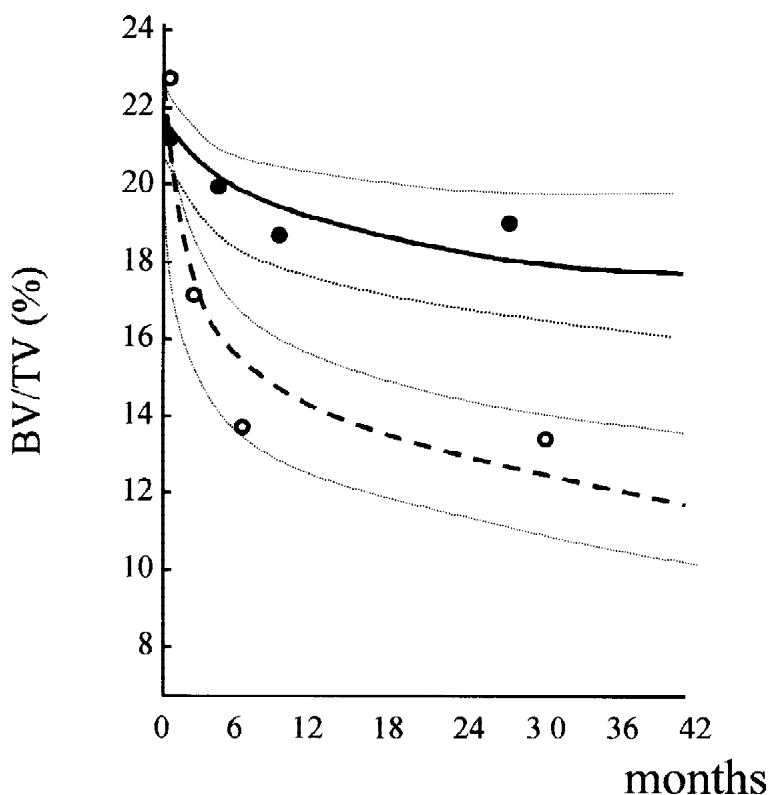
pay a high price - especially in terms of bone mass - for the long-term glucocorticoid therapy which they require. In children who have undergone a transplant operation deflazacort has been found to be well tolerated and to prevent glucocorticoid-induced bone loss (28, 29). In adult patients, using deflazacort instead of prednisone was associated with a bone-sparing effect of 6% at the lumbar spine (30), which would correspond to a reduction by approximately 1.4-fold in the risk of vertebral fractures (31).

At variance with all of the data so far reported is the result of a double-blind study in 30 patients with polymyalgia rheumatica, which showed no difference in bone mineral density between the prednisolone and deflazacort groups at 6 and 12 months, thus failing to demonstrate the existence of any calcium sparing properties in deflazacort (32). This discrepancy could be attributable to the low sensitivity of BMD in assessing changes in trabecular bone mass. As pointed out earlier, densitometric measurements of the lumbar spine represent a mix of trabecular vertebral bone and cortical bone of the posterior arch, the latter being particularly relevant in elderly people, such as those studied by Krogsgaard (32).

All in all, there is evidence that deflazacort, when used at an equipotent dosage, causes less severe side effects than prednisone, particularly with regard to bone metabolism and mass. The crucial issue is the dose equivalence of the two compounds, because fewer unwanted effects may also be associated with lower therapeutic activity.

#### Dose equivalence of prednisone and deflazacort

The appropriate ratio of doses for bioequivalence in the case of prednisone and deflazacort has been established in a number of studies which demonstrated that deflazacort is approximately 25% less potent than prednisone in terms of absolute dosage. In normal subjects bioequivalence, assessed with respect to the capacity to inhibit T cell reactivity, appeared to be 1: 1.2 (33). As estimates of potency are difficult to evaluate in patients with disease, the concept of the "minimum effective dose" has been ex-



**Fig. 1.** Pattern of trabecular bone loss in 12 pairs of patients (not previously treated with glucocorticoids) as modelled by the two functions found for deflazacort (heavy continuous lines) and prednisone (heavy dotted lines) (ref. 6).

tensively used.

Based on the results of 7 trials using various designs (double-blind, crossover studies, paired patients studies and between-patients studies) and involving 160 patients, Avioli estimated the potency ratio of deflazacort to prednisone to be 1.28 to 1 (1.17 - 1.38, 95% CI) (34). He also determined the bone wasting ratio (the ratio between bone loss velocity values observed in patients given the minimum effective doses of two glucocorticoids) of prednisone to deflazacort and found it to be approximately 2.03: 1 (1.84 - 2.23, 95% CI). In the clinical setting, the equivalence ratio of deflazacort and prednisone seems to depend upon the disease involved. It has been shown to be about 1.2 in immunomediated disease (24, 35), nephrotic syndrome (36) and in kidney transplant patients (30, 37), but 1.4 in polymyalgia rheumatica, a disease in which the clinical suppression of inflammatory disease can increase the dose ratio up to 1.7 (38). It is surprising that this study showing that the antiinflammatory equipotency between deflazacort and prednisone is closer to 1.4 than to 1.2 has been interpreted as strong evidence against the previous estimated potency ratio (39).

The difficulties of establishing equipotency ratios for glucocorticoids have been highlighted by the results of a recent study (40) in which healthy subjects were given several doses of deflazacort and prednisone, and the equivalent dose ratios were calculated for the suppression of eosinophils (1.14), osteocalcin (1.54), cortisol (2.27), and lymphocytes (2.77). The study sheds doubt upon the equipotency of the suggested dose ratio (1.3), but underlines as well that there may be a different "sensitivity" of tissues and cells to the 2 glucocorticoids studied.

In summary, although a few findings cast doubt on the generally assumed equipotency dose ratio between prednisone and deflazacort, it seems inappropriate to suggest that the available literature on undesirable effects, including the more recent data on kidney transplant patients, may be invalid because they have perhaps compared not exactly equivalent doses of the two glucocorticoids (41). Most probably the equivalence ratio also depends on the disease; in fact, discrep-

ancies have been found only in polymyalgia rheumatica.

## Conclusions

Deflazacort is an oral glucocorticoid which is approximately 25% less potent than prednisone in terms of absolute dosage. Histomorphometry and densitometry studies have proven that, when used at doses with approximately equivalent anti-inflammatory efficacy, it causes less loss of bone mass than prednisone. However, much of the data on the bone-sparing effect of the drugs come from trials that are relatively small or of short duration. Therefore, well-designed clinical trials are needed, especially to clarify the appropriate ratio of doses for bio-equivalence with prednisone.

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