Glucocorticoid osteoporosis – mechanisms and management

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Abstract

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 Bone loss is reversible when glucocorticoid treatment is withdrawn.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

Introduction

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

Actions of glucocorticoids on bone and calcium metabolism

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

Osteoblasts

The osteoblast is one of the bone cells principally affected by glucocorticoids. Many of the effects are directly mediated through the osteoblast’s glucocorticoid receptor, resulting in increased differentiation of osteoblast precursor cells but reduced proliferation and matrix synthesis in mature osteoblasts. In particular, the mRNAs for type I collagen (1) and the principal non-collagenous protein of bone, osteocalcin (2), are reduced by glucocorticoids, which also modulate mRNAs for osteopontin, fibronectin, β1-integrin, bone sialoprotein and the insulin-like growth factors (3). The activity of the last of these factors is modulated by the concentrations of both stimulatory and inhibitory binding proteins, which are themselves influenced by glucocorticoids in a way that reduces the growth-stimulatory activity of these factors (4, 5). These changes in the activity of individual osteoblasts are reflected in changes in bone histomorphometry which, in both animal and human studies, consistently demonstrates that glucocorticoid treatment is associated
with reduced rates of bone formation and reduced periods of bone formation within each remodelling cycle (6). This reduction in bone formation is detectable clinically by reduced circulating concentrations of osteocalcin (7) and the C-terminal pro-peptide of type I pro-collagen (8), both markers of osteoblast activity.

**Osteoclasts**

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

**Intestinal absorption of calcium**

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

**Urinary excretion of calcium**

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

**Vitamin D**

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

**Parathyroid hormone**

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

**Phosphate metabolism**

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

**Sex hormones**

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

**Bone density in glucocorticoid-treated patients**

Exposure to supraphysiological doses of glucocorticoids leads to a substantial and rapid loss of bone. The limited prospective data available suggest that bone loss takes place in virtually all individuals (27, 28). Bone loss is most marked in the first 12 months (29), but continues long term, albeit at a lower rate (30). A prospective study has shown an 8% decrement in the trabecular
bone of the lumbar spine after 20 weeks of treatment with prednisone in a mean dose of 7.5 mg/day (28). Cross-sectional studies in patients treated for periods of 5 years show that integral bone mass of the lumbar spine and proximal femur is 20% below control values (31). Bone loss occurs more rapidly in trabecular than in cortical bone and decrements approaching 40% are seen in cross-sectional studies of the trabecular bone of the lumbar spine, whether assessed by quantitative CT scanning (32) or by dual energy x-ray absorptiometry in the lateral projection (33). Concern has been expressed that some of this apparent bone loss is artefactual, arising from the altered distribution of fat, particularly marrow fat, in the presence of steroid excess. There is little evidence that marrow fat is changed in Cushing’s syndrome (34), and the bone loss observed in studies using either dual energy CT scanning (28) or bone biopsies (29) is similar to that found with single energy CT and dual energy x-ray absorptiometry, implying that soft-tissue changes do not have a significant influence on the changes found with the latter techniques.

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

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

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

Incidence of fracture in glucocorticoid-treated patients

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

Fracture prevention

General measures

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

Calcium

The deleterious effects of glucocorticoids on calcium transport in both the gut and renal tubule suggest that the administration of high doses of oral calcium might significantly improve bone mass. Unfortunately, there is little experimental evidence to support this contention. Nilsen et al. (46) demonstrated a slight reduction in the rate of radial bone loss in patients with rheumatoid arthritis who were given 6 g/day hydroxyapatite. Reid and Ibbertson (47) demonstrated significant suppression of bone resorption (measured as hydroxyproline...
excretion) with 1 g/day elemental calcium supplementation. However, in a number of prospective studies in which calcium supplements of this magnitude were administered to the control groups, it has been shown that calcium alone will not prevent steroid-induced bone loss (48–50). This implies that steroid osteoporosis is not merely a problem with mineral balance, but is primarily related to reduced bone matrix synthesis, comparable to the wasting that occurs in soft tissues such as skin and muscle. Thus the therapeutic task is not merely to provide more substrate for bone synthesis, but also to reverse the catabolic effects of glucocorticoids on the skeleton.

**Sex hormones**

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

In steroid-treated men, circulating testosterone concentrations are reduced by almost 50% — a factor likely to contribute to the development of osteopenia. We have recently shown that testosterone replacement produced a 5% increase in lumbar spine bone mineral density after 12 months, in addition to reversing the accumulation of body fat and loss of lean tissue that accompany steroid treatment (57). Androgens, in the form of anabolic steroids, have also been used for treating steroid-induced osteoporosis. They would seem to have little benefit, but also to reverse the catabolic effects of glucocorticoids on the skeleton.

**Bisphosphonates**

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

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

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

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

**Vitamin D and its metabolites**

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

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

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

**Fluoride**

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

**Calcitonin**

Calcitonin acts via specific receptors on osteoclasts, reducing bone resorption. It has been used in some countries for the management of postmenopausal osteoporosis, though its effectiveness is generally less than that of hormone replacement therapy or the bisphosphonates. There have now been several controlled trials in steroid-treated patients that suggest that it slows bone loss. Thus Rizzotto et al. (79) found that injections of salmon calcitonin (100 IU every 1–2 days) prevented bone loss over a 15-month period, whereas vertebral bone mass declined 14% in the control group. Using a similar regimen, Luengo et al. (80) found an increase in spinal bone density of 4% in those receiving calcitonin, whereas this index decreased by 2.5% in the control group over a 12-month period. Similar results
using intranasal calcitonin have been reported by Montemurro et al. (81). Thus calcitonin is likely to be effective, but its side effects and cost make it less attractive than sex hormone therapy or the bisphosphonates.

**Thiazides**

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

**Bone-sparing glucocorticoids**

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

**Who to treat**

Many patients receiving steroid treatment do not develop fractures, whereas others will suffer a fracture within a few months of beginning these drugs. As outlined above, there is a wide range of potential treatments so the clinician requires strategies for selecting the appropriate intervention, if any, for each patient. The patients who should be treated with drugs that increase bone mass are those at highest risk of fracture. A past history of fractures after minimal trauma is clearly an indication for treatment. The other clinical risk factors for low bone mass are listed above but, if possible, it is desirable that bone density should be measured directly. A bone density below the young adult normal range (i.e. more than 2–2.5 standard deviations below the young normal mean) indicates that that patient's immediate risk of fracture is significantly increased: each standard deviation change in bone density is associated with a twofold change in fracture risk. Patients whose bone density is in the lower one-third of the normal range may not be at immediate risk of fracture, but will become so if they continue treatment in the long term, or if there are other risk factors present (such as high glucocorticoid dose or concurrent sex hormone deficiency). Thus all these individuals should be considered for some bone-protective treatment.

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

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

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The text contains references to various medical studies and clinical trials related to the effects of corticosteroids on bone health, with a focus on osteoporosis and its prevention. It discusses the use of corticosteroids in rheumatic diseases and the impact on bone density, including the role of calcium, vitamin D, and other supplements in preventing bone loss. The text also references studies on the effectiveness of bisphosphonates, estrogen/progesterone therapy, and other hormone replacement therapies in managing steroid-induced osteoporosis. Additionally, it touches on the prevention and management of bone loss in patients with chronic diseases such as sarcoidosis and asthma. The references span from 1976 to 1996, covering a period of 20 years, indicating the evolution of understanding and treatment strategies in this area.


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