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INTRODUCTION

Corticosteroids are widely used in primary care. The main conditions requiring them include rheumatoid arthritis, polymyalgia rheumatica, inflammatory bowel disease and asthma/chronic obstructive airways disease, and around 0.5% of the UK adult population currently take oral corticosteroids. Although therapeutically effective, their long-term use is associated with considerable morbidity and possibly also premature mortality, for example through accelerated atherosclerosis. In the locomotor system, however, the principal steroid complication is the development of osteoporosis.

The pathogenesis of corticosteroid-induced osteoporosis is multifactorial. Corticosteroids reduce osteoblastic activity, and the resulting osteoblastic/osteoclastic imbalance causes net loss of bone. Corticosteroids also reduce intestinal calcium absorption and lower the circulating sex steroid levels (the latter due to effects on the hypothalamic-pituitary axis and gonads). These effects are over and above those of the disease for which the corticosteroids are being prescribed, and which may itself be associated with bone loss, e.g. Crohn’s disease, active rheumatoid arthritis.

EFFECT OF CORTICOSTEROIDS ON BONE

Bone mass

The level of bone mass is a major determinant of bone strength – and thus susceptibility to fracture – and corticosteroid therapy is associated with bone mass reduction. The degree of corticosteroid-induced bone loss is greatest at skeletal sites with a high trabecular bone content – particularly the spine and ribs, although other sites are also affected. Bone loss is most rapid during the first 6–12 months of therapy, though it continues more slowly thereafter. The degree of bone loss is related to both dose and duration of corticosteroid usage, although there is wide inter-individual variation in the rate of bone loss. Corticosteroid-induced bone loss is at least partially reversible, though recovery may be slow following steroid withdrawal.

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Fracture
As with bone mass reduction, the risk of fracture increases with both dose and duration of therapy. Observational studies suggest that around 30% of individuals taking long-term corticosteroids (i.e. >3–5 years) will have evidence of osteoporotic vertebral fractures, while the risk of hip fracture is increased 2-fold. Despite these observations, various surveys confirm that only a minority of patients taking oral steroids (about 15%) are co-prescribed therapy to prevent or minimise bone loss and fractures.

Based on current evidence it is unclear whether there is a ‘safe’ minimum dose of corticosteroids, i.e. that below which there is no osteoporosis risk. However, there is a consensus view that suggests daily doses at or above 7.5 mg pose a significant threat to skeletal health, if continued for ≥6 months.

DIAGNOSING OSTEOPOROSIS
Osteoporosis is asymptomatic in the absence of fracture. A reduction in bone mass may be suspected from plain radiographs, but radiographic ‘osteopenia’ is an inaccurate indicator of underlying osteoporosis. Bone densitometry is currently the optimal method for diagnosing osteoporosis. A variety of techniques for measuring bone mass are now available, though dual energy x-ray absorptiometry (DEXA) of the spine and hip is the most widely used. DEXA can additionally be used to assess prognosis (future fracture risk) and the need for antiporotic therapies, as well as for monitoring such therapies.

Those at greatest risk of corticosteroid-induced osteoporosis and fractures are the elderly. Vertebral fractures are often clinically silent. Furthermore, back pain, which is the usual presenting symptom of vertebral fracture, is non-specific. A high index of clinical suspicion is therefore necessary in patients taking corticosteroids, particularly those who present with new back pain symptoms, even if mild or atypical for vertebral fracture. Radiographs of the thoracic and/or lumbar spine are necessary to confirm osteoporotic vertebral fracture. Other symptoms of vertebral osteoporosis, including height loss and dorsal kyphosis, occur late in the natural history, and when osteoporosis is already advanced. Peripheral (limb) fractures typically present with acute onset of pain following an episode of trauma, such as a fall, although in osteoporotic patients the trauma involved may be surprisingly small – hence the term ‘minimal trauma’ or ‘fragility fracture’.

PREVENTION AND MANAGEMENT
Current and prospective users of long-term oral corticosteroids should be educated regarding the potential osteoporosis risk. Clearly, for those already taking corticosteroids the regime should be constantly reviewed, and dosage reduced where possible. Consideration should also be given regarding alternative routes of steroid administration (e.g. inhaled corticosteroids in asthmatic patients). In some cases introducing steroid-sparing disease-suppressing agents (e.g. azathioprine, methotrexate) may allow a reduction in the steroid dose. All patients should be given advice about modifying lifestyle factors known to adversely affect bone mass, including stopping smoking, avoiding excess alcohol consumption, doing regular weight-bearing exercise and maintaining an adequate level of calcium intake.

Calcium and vitamin D supplementation should be given if the diet is deficient, or in high-risk groups such as the housebound or elderly. Some calcium supplements may be poorly tolerated, in which case alternative preparations should be tried. Calcium/vitamin D malabsorption may represent a specific separate issue, for example in Crohn’s disease. Hormone replacement therapy (HRT) may also be considered generally beneficial for general skeletal health in peri- and postmenopausal women, who should be encouraged to continue it when steroids have been commenced.

INDICATIONS FOR TREATMENT
Treatment should be considered for all patients who are about to commence or are currently taking ≥7.5 mg per day of prednisolone (or equivalent dose of another corticosteroid) for a period of ≥6 months.

(i) Patients commencing higher corticosteroid doses (>15 mg prednisolone or equivalent), where this will be used for ≥6 months, should be offered bone protection from the onset of such treatment. Patients who have already taken prolonged high doses without bone protection should be offered this forthwith.

(ii) Patients commencing intermediate steroid doses (7.5–15 mg prednisolone) in whom one or more concurrent risk factors for osteoporosis are present (see Table 1) should also be offered bone protection from the onset of steroid treatment. Patients with concurrent risks who have already taken prolonged intermediate doses without bone protection should be offered this forthwith.

In clinical situations (i) and (ii), DEXA is unnecessary to confirm the need for bone protection, though if available it may be useful as a method of monitoring treatment.
(iii) Patients commencing intermediate steroid doses (7.5–15 mg prednisolone) but who have no concurrent risk factors are at lower osteoporotic risk. In such patients DEXA may be used to determine the fracture risk, and thus the need for and timing of onset of bone-protective therapy. The threshold value of bone mineral density (BMD) for intervention is somewhat arbitrary. There is a consensus view (as outlined in UK national guidelines – see ‘Further reading’) that antiporotic treatment should commence when the ‘T-score’ falls below –1.5 at the spine and/or hip (i.e. 1.5 standard deviations below the mean value of BMD in healthy young adults). Where BMD is greater than the threshold for intervention, withholding specific protective therapy is justifiable, though DEXA should be repeated in 12 months.

TREATMENT OPTIONS

Hormone replacement therapy

It is assumed that the general measures outlined above have been implemented. HRT is the treatment of choice for peri- and postmenopausal women, although specific risk factors may preclude its use, e.g. previous breast cancer, recurrent thromboembolism. In men, testosterone should be considered if hypogonadism is proven.

Bisphosphonates

It is assumed here that the general measures outlined above have been implemented. Bisphosphonates are effective at preventing and treating corticosteroid-induced bone loss. Bisphosphonates may be used in those who are eugonadal or in postmenopausal women who are unwilling or unable to take HRT. There is no specified age limitation to bisphosphate use, and they can be safely prescribed to elderly patients already taking dietary calcium/vitamin D supplements. In the UK the most widely used oral bisphosphonates are etidronate, alendronate and risedronate. These drugs are generally well tolerated, though mild gastrointestinal side-effects may occur. In the case of cyclic etidronate treatment, side-effects are more often related to the calcium supplements used. Alendronate therapy may be associated with oesophagitis, and the drug should thus be avoided in those with known oesophageal problems. Oral bisphosphonates should be taken on an empty stomach, because of the possibility of food impairs absorption of the drug.

Calcitriol

Calcitriol should be considered in patients who are unable to tolerate bisphosphonates, or for younger patients in whom safety is a concern. Its use, however, may be complicated by hypercalcaemia, and regular monitoring of serum calcium is necessary.

Oestrogen analogues

Raloxifene is an oestrogen receptor agonist in bone, and may thus represent a useful bone protective agent. However, evidence for its use in preventing or treating corticosteroid-induced osteoporosis is currently unavailable. Further research is needed to elucidate the place of oestrogen analogues in prevention or treatment.

If facilities are available, bone densitometry may be used to monitor the effects of treatment. If there is evidence of significant bone loss while taking treatment (annual loss >4% at the spine and/or 7% at the hip) an alternative therapy should be considered, and/or referral to a specialist.

MANAGEMENT OF OSTEOPOROTIC VERTEBRAL FRACTURE

Most patients with symptomatic vertebral fracture can be managed in the primary care setting. The initial goal of treatment is to alleviate pain, followed by measures to reduce future fracture risk. Patients should therefore avoid other than short-term bed rest, as immobility increases bone loss. Patients should also be given information on back care, including gentle back-strengthening exercises. Flexion exercises should be avoided as these may risk further vertebral fracture. If the initial pain is very severe, and patients are rendered unable to self-care or become bed-bound, hospital admission may be necessary. Even then, early mobilisation is still important.

The presence of an existing vertebral fracture statistically increases the risk of subsequent osteoporotic fractures considerably, so it is important that patients with established fractures receive full and appropriate antiporotic treatment promptly, if not already doing so. Patients who sustain fragility fractures while taking corticosteroids should have investigations to identify other contributory causes of osteoporosis, including occult hyperthyroidism, hypogonadism and malignancy (see Table 2).

WHEN TO REFER TO HOSPITAL

For current and prospective corticosteroid users, referral to a specialist unit is indicated if assistance is needed.
TABLE 2. Investigations for other causes of osteoporosis.

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<th>Investigation</th>
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<td>Full blood count (FBC)</td>
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<tr>
<td>Erythrocyte sedimentation rate (ESR)</td>
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<tr>
<td>Calcium and alkaline phosphatase</td>
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<td>Thyroid function tests</td>
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<tr>
<td>Protein electrophoresis</td>
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<tr>
<td>Testosterone (in men)</td>
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<tr>
<td>Estradiol (in amenorrhoeic, premenopausal women)</td>
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with assessing the need for bone protection (e.g. assessing fracture risk), establishing the diagnosis of osteoporosis, or osteoporosis management. Thus, depending on local circumstances, referral may be necessary for access to DEXA. Children, adolescents and younger adults requiring long-term, higher-dose steroid therapy pose particular management difficulties. Such cases are best managed with a ‘shared care’ approach – i.e. by physicians with an interest in metabolic bone disease, in collaboration with patients’ general practitioners.

CONCLUSION

Osteoporosis is a serious and often neglected complication of corticosteroid therapy. Increased awareness of the problem in primary and secondary care, with early intervention for those at risk, should help reduce the significant morbidity associated with corticosteroid-induced osteoporosis.

FURTHER READING


USEFUL ORGANISATION

National Osteoporosis Society (NOS)
www.nos.org.uk

ADDENDUM (August 2005)

Since publication of this report in May 2001 there have been important developments concerning the prevention and treatment of corticosteroid-induced osteoporosis.

Epidemiology

Evidence from a recent meta-analysis suggests that oral corticosteroid therapy of 5 mg daily (of prednisolone or equivalent) leads to a reduction in bone mineral density and a rapid increase (within 3–6 months) in the risk of fracture during the treatment period.1 In a large retrospective cohort study there was evidence that even lower doses (<2.5 mg prednisolone) are linked with an increased risk of vertebral fracture.2 Corticosteroids appear to contribute to the increase in fracture risk over and above the effect of low bone mineral density (BMD).3 Thus, for a given BMD, the risk of fracture is higher in corticosteroid-induced osteoporosis than in postmenopausal osteoporosis.

Therapy

Recent data suggest an increased vascular risk linked with hormone replacement therapy4 and this is no longer considered as first-line therapy in the prevention or treatment of corticosteroid-induced osteoporosis. Beneficial effects on BMD in the spine and hip have been demonstrated for several pharmacological interventions.5 Fracture has not been a primary endpoint of any studies of prevention or treatment of corticosteroid-induced osteoporosis; however, a reduction in vertebral fracture risk has been observed in post hoc or safety analyses of trials of etidronate, alendronate and risedronate.

Guidelines

New national guidelines for prevention and treatment of corticosteroid-induced osteoporosis have been published.4 In these guidelines, men and women should be considered for prevention measures if there is a commitment or exposure to oral corticosteroids (any dose) for a period of 3 months or longer. Individuals at high risk, including those aged 65 years and over and those with a prior fragility fracture, should be advised to commence bone protective therapy at the time of starting corticosteroids – measurement of bone density is not required before starting treatment. In others, in whom it is intended to continue therapy for at least 3 months, bone densitometry (using dual energy x-ray absorptiometry) should be considered. Based on bone mass measurements the guidelines suggest that a T score of −1.5 or lower may indicate the need for intervention with a bone sparing agent. For those with a T score between 0 and −1.5 repeat BMD should be performed in 1–3 years if the corticosteroids are continued.