Leading article

Management of bone disease in patients on long term glucocorticoid therapy

Osteoporosis is a well documented complication of gastro-intestinal disease. Its pathogenesis is multifactorial but glucocorticoid therapy is likely be an important contributory factor, particularly in patients with inflammatory bowel disease.[1] A widely recognised condition, glucocorticoid induced osteoporosis is under diagnosed and often inadequately treated. Two recent surveys, one from a large teaching hospital[2] and one community based,[3] reported that only a small minority of patients receiving long term glucocorticoid therapy were offered prophylaxis against bone loss. However, recent evidence shows that intervention can prevent bone loss and reduce the significant morbidity associated with glucocorticoid induced osteoporosis.[4 5] This emphasises the need to adopt a more aggressive approach towards prevention of osteoporosis, and to define management strategies for patients who are treated with glucocorticoids.

Characteristics of glucocorticoid induced bone loss
The time course of glucocorticoid induced bone loss has not been well documented but there is evidence that the rate of loss is most rapid in the first six to 12 months of treatment and decreases thereafter.[6 7] If these findings are confirmed, there are clear implications for the timing of intervention. Although not all studies are in agreement, most data indicate that the spine and proximal femur are affected similarly[8] and observational studies suggest that the risk both of hip and vertebral fractures is higher in patients treated with glucocorticoids.[9 10] Data from placebo controlled primary prevention trials indicate rates of bone loss in untreated patients in the region of 2–4% each year, both in the spine and proximal femur.[4 11] This is considerably in excess of rates of bone loss expected in a healthy population of similar age and sex distribution.

Attempts to show a correlation between the dose and duration of glucocorticoid therapy, and bone loss, have produced conflicting results. This may partly reflect the confounding effect of disease activity, as improvement in disease status due to glucocorticoid therapy may have beneficial effects on bone mass. Furthermore, accurate calculation of the cumulative dose of glucocorticoids in individuals is often difficult, and other factors may be involved in bone loss, particularly other medications; there is also considerable variation between individuals in skeletal response to glucocorticoids. Overall, however, higher doses are more likely to be associated with greater bone loss. Whether there is a "safe" minimum dose below which there is no bone loss has not been established; there is some evidence that daily doses of prednisolone lower than 7.5 mg do not have any adverse effect[12] but this finding has not been universal.[13]

Studies of patients with Cushing's syndrome show that bone loss associated with glucocorticoid excess is at least partially reversible,[14] although recovery is slow. This may have important implications for patients treated with intermittent courses of glucocorticoids as there may be the potential for some reversal of bone loss during periods off treatment, although this requires further study. Oral budesonide or topical large bowel preparations of glucocorticoids have not been reported as causing clinically significant, adverse skeletal effects; a recent study observed no changes in bone mineral density in 20 patients treated with budesonide for two years.[15] Finally, dosing on alternate days does not seem to have any advantage over daily dosing in terms of adverse effects on the skeleton.[16]

Pathogenesis of glucocorticoid induced osteoporosis
The pathogenesis of glucocorticoid induced bone loss is complex and multifactorial.[17 18] In vitro data show that supraphysiological concentrations of glucocorticoids inhibit osteoblast proliferation and differentiation, and stimulate osteoblast apoptosis; additionally, reduced expression of type I collagen, osteocalcin, insulin-like growth factor-1 (IGF-1), and IGF binding proteins 3 and 5, which enhance IGF-1 activity, has been demonstrated. Glucocorticoids also decrease transforming growth factor β (TGF-β) activity, with an increase in binding to non-signalling receptors. As well as these direct suppressive effects on bone formation, bone resorption is increased by predominantly indirect actions including hyperparathyroidism secondary to reduced intestinal calcium absorption, and hypogonadism resulting from glucocorticoid induced effects on the hypothalamic–pituitary axis and gonads. High doses of glucocorticoids also decrease renal tubular phosphate reabsorption and increase the synthesis of 1,25-dihydroxyvitamin D.[19]

Pathophysiology of glucocorticoid induced bone loss
The cellular mechanisms of glucocorticoid induced bone loss have not been clearly defined. Studies in patients established on long term glucocorticoid therapy have shown reduced bone turnover and decreased bone formation at the cellular level,[20] but in view of the rapidity of bone loss in the early stages of treatment it is likely that, at least initially, increased bone turnover and resorption also contribute to bone loss. The effectiveness of anti-resorptive treatment in the primary prevention of glucocorticoid induced bone loss would be consistent with this hypothesis.

The alterations in bone remodelling that are responsible for bone loss have important implications for the associated structural changes in cancellous bone, which influence bone fragility and risk of fracture. Although it has been suggested that trabecular thinning rather than penetration is the predominant consequence of glucocorticoid induced bone loss,[21] this has not been established definitively and further studies are required. Whether the relation between bone mass and fracture risk in patients treated with glucocorticoids is the same as that characterised in the healthy aging population is also relevant to this issue. Indirect evidence indicates that fracture occurs at a higher bone den-

Abbreviations used in this paper: IGF, insulin-like growth factor; TGF, transforming growth factor.

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sity in glucocorticoid induced osteoporosis than in postmenopausal osteoporosis[22]; this would be consistent with greater disruption of bone architecture in glucocorticoid induced osteoporosis. Alternatively, glucocorticoid administration may result in specific alterations in bone matrix or mineral composition, or both.

Management of glucocorticoid induced osteoporosis

Intervention in patients receiving glucocorticoids involves primary prevention, in which prophylaxis is administered at the start of glucocorticoid therapy, and secondary prevention, in which the bone active agent is given to glucocorticoid treated patients with reduced bone mineral density and/or those who develop a fragility fracture. The dose (and to a lesser extent the duration) of glucocorticoid therapy is the criterion for intervention at the primary prevention stage; the presence of additional risk factors for osteoporosis also affects management decisions. Reduced bone mineral density and/or incident fragility fractures are used as selection criteria for secondary prevention.

Whenever possible, bone mineral density measurements should be obtained in the hip and spine using dual energy *x* ray absorptiometry in order to provide a baseline against which to monitor the effects of intervention and to aid treatment decisions in patients being considered for secondary prevention. Lateral *x* rays of the thoracic and lumbar spine should also be obtained to assess the presence of prevalent vertebral fractures. Where appropriate, other secondary causes of osteoporosis should be excluded, particularly in patients with a previous or prevalent fragility fracture.

Indications for primary and secondary prevention

Primary prevention should be considered in all patients receiving high doses—for example, 15 mg/day prednisolone or equivalent, for three months or more. Patients treated with lower doses (between 7.5 and 15 mg prednisolone daily), having one or more other strong risk factors for osteoporosis, should also be offered primary prevention. Other risk factors for osteoporosis include age over 65 years, previous or prevalent fragility fracture, family history of fragility fracture, premature menopause (at age 45 years or younger), premenopausal amenorrhoea, and low body weight. Bone mineral density measurements are not required to make decisions about primary prevention, although they are useful as a means of monitoring the effects of treatment.

Secondary prevention should be considered in those patients who have not been offered primary prevention, and who are receiving 7.5 mg daily or more of prednisolone, if bone mineral density is low and/or fragility fracture occurs during glucocorticoid treatment. Interventional thresholds based on bone mineral density are arbitrary; a T score at the hip and/or spine below −1.5 (that is, 1.5 standard deviations below the mean value in healthy young adults) has been suggested as an appropriate threshold, and is consistent with recently developed European regulatory recommendations.[23] In patients who continue to require glucocorticoid therapy, but who have a T score above this level, bone densitometry should be repeated annually and treatment instituted if the bone mineral density T score subsequently falls to below −1.5.

Pharmacological interventions: general considerations

The primary aim of intervention is to reduce fracture rate. In treatment studies, the value of bone mineral density as a surrogate for fracture risk is increasingly being challenged, and thus direct demonstration of fracture reduction is required before efficacy can be proved. Presently, no randomised clinical trials with fracture as the primary end point have been reported, although favourable trends in vertebral fracture reduction have emerged from randomised controlled trials in which bone mineral density was the main outcome measure.[4 5] As yet, no fracture data are available for the hip or other non-vertebral sites.

A number of agents, including bisphosphonates, hormone replacement treatment, calcium and vitamin D, calcitriol, calcitonin, and sodium fluoride, have been evaluated in patients receiving glucocorticoid therapy.[24] Bisphosphonates provide the strongest evidence to date[4 5]; although only cyclical etidronate is licensed for prevention and treatment of glucocorticoid osteoporosis in the United Kingdom, other bisphosphonates are likely to follow in the near future. The data currently available suggest that bisphosphonates are effective both in the primary and secondary prevention of glucocorticoid induced osteoporosis; the duration of previous glucocorticoid therapy does not seem to affect the response to treatment, at least in terms of bone mineral density.[5] It should, however, be emphasised that none of these studies has specifically targeted patients with inflammatory bowel disease and other gastrointestinal disorders, and few such patients have been included in the clinical trials reported to date.

Cyclical etidronate treatment consists of a regimen of 400 mg of etidronate daily for two weeks, followed by 500 mg calcium daily for 76 days; this three month cycle is then repeated. Alendronate is given as a single daily dose of 10 mg without a calcium supplement although supplementation is advised in patients with a low dietary calcium intake. In the majority of treatment studies, the follow up period has not exceeded one year, and longer term studies are required before the optimal duration of treatment can be established. In general, however, treatment should be continued at least until glucocorticoids are withdrawn, or reduced to a dose lower than 5 mg prednisolone daily.

Bone densitometry should be used to monitor the effects of treatment at yearly intervals; this is particularly important in subjects with gastrointestinal disease because of the lack of data in this patient group, and specific concerns about the intestinal absorption of bisphosphonates, which is low even in normal subjects.

Bisphosphonates are generally well tolerated and adverse effects are usually mild. Gastrointestinal signs include nausea, diarrhoea and abdominal pain, and, in the case of cyclical etidronate treatment, are often related to calcium supplements. Alendronate treatment may occasionally be associated with severe oesophagitis[25] and, thus, should not be given to patients with existing oesophageal disease. This is particularly important as glucocorticoid therapy increases the risk of upper gastrointestinal disease. In those patients who are unable to tolerate bisphosphonates, calcitriol should be considered.[7] This is given in a dose of 0.5–1.0 μg daily; hypercalcaemia may occur and regular monitoring of serum calcium is necessary in treated patients.

General measures

In patients treated with glucocorticoids, the dose required should be constantly reviewed and kept to a minimum. In some cases, introduction of other disease suppressing agents may allow a reduction in the dose of glucocorticoid. Modification of life style measures known to affect skeletal health should be noted—for example, physical activity should be promoted, adequate nutrition ensured, and cigarette smoking discouraged. The use of deflazacort may be associated with reduced adverse skeletal effects, but this has yet to be established definitively. Based on its lower systemic absorption, budesonide may be less harmful to the skeleton than prednisolone,[26] but further studies are needed to confirm this.

CALCIUM AND VITAMIN D SUPPLEMENTATION

Evidence of the effects of calcium and vitamin D supplementation on glucocorticoid induced bone loss is conflicting,[27][28] but, supplements should be advised, particularly in patients with malabsorption at risk of vitamin D deficiency, and in those with a low dietary calcium intake. The recommended daily dose of elemental calcium is approximately 1 g and of vitamin D 800 IU; higher doses of vitamin D may be required in some patients with small intestinal disease, and occasionally parenteral vitamin D (150 000–300 000 IU once every one to three months). Alternatively, oral administration of the active metabolite 1,25(OH)2D3 (calcitriol), or its analogue 1α-hydroxyvitamin D3 (alfacalcidol) may be given, although regular monitoring of serum calcium is required because of the risk of hypercalcaemia. The usual dose is between 0.5 and 1.0 µg daily.

HORMONE REPLACEMENT TREATMENT

Hypogonadism may occur both as a result of glucocorticoid therapy and as a consequence of chronic liver disease, inflammatory bowel disease, and other causes of malabsorption. It affects the skeleton adversely and, as there is evidence[29][30] that oestrogen or testosterone replacement reduces bone loss in hypogonadal patients receiving glucocorticoid therapy, it seems rational to advise hormone replacement treatment in all patients with evidence of hypogonadism, including postmenopausal women. Transdermal preparations are available both for oestrogen (and progestin if required) and testosterone and, in patients with chronic liver disease and intestinal malabsorption, are preferred to oral treatment.

Conclusion

Osteoporosis is an important but often neglected complication of glucocorticoid therapy. Recent evidence indicates that bisphosphonates are effective in the primary and secondary prevention of glucocorticoid induced osteoporosis; primary prevention should be offered to patients receiving high doses of glucocorticoids and those who, although on lower doses, have additional risk factors for osteoporosis. Secondary prevention should be advised for other patients on glucocorticoid treatment on the basis of low bone mineral density or incident fragility fractures. Calcium and vitamin D supplements should be given when indicated, and hormone replacement treatment should be advised in hypogonadal patients. There is still a paucity of data on the prevention of glucocorticoid induced osteoporosis in patients with gastrointestinal disease and further studies are required, particularly in view of potential concerns about intestinal absorption of bisphosphonates in such patients.

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