Emerging Consensus on Prevention and Treatment of Glucocorticoid-induced Osteoporosis

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Current Rheumatology Reports 2007, **9:**78–84
Current Medicine Group LLC ISSN 1523-3774

Glucocorticoid-induced osteoporosis is a common but still relatively neglected problem, with a low level of awareness among primary and secondary care physicians. Fractures appear early after initiation of treatment, and effective prophylaxis requires primary prevention in those at high risk of fracture. Bisphosphonates are the treatment of choice, and calcium and vitamin D supplements are also indicated in the majority of individuals. Organized care programs together with the use of evidence-based guidelines have the potential to improve significantly the management of this serious complication of glucocorticoid therapy.

Introduction

The association between glucocorticoid excess and osteoporosis has been known for many decades, but its importance in clinical practice has only recently been recognized. The rapidity of bone loss after initiation of glucocorticoid therapy, together with the associated increase in fracture risk, has emphasized the importance of primary prevention in individuals at high risk of fracture and the need for specific care protocols for these patients. A number of pharmacologic agents have been evaluated for the prevention and treatment of glucocorticoid-induced osteoporosis, although the evidence base remains weaker than that for postmenopausal osteoporosis.

Epidemiology

Despite the widespread use of glucocorticoids in medicine, awareness of the morbidity associated with glucocorticoid-induced osteoporosis is relatively low. A study utilizing data from the U.K. General Practice Research Database documented a prevalence of current oral glucocorticoid use of 2.5% in individuals 70 to 79 years old. The most frequently recorded indication was respiratory disease, and connective tissue disease and dermatologic conditions are also responsible for significant use. Only approximately 5% of oral glucocorticoid users were prescribed bone protective medications [1].

Many studies have documented the association between glucocorticoid therapy and fracture risk [2–5]. The risk of both hip and vertebral fractures is increased even at daily doses of prednisolone as low as 2.5 to 7.5 mg, with fracture risk increasing with daily dose [6]. Some relationship also seems to exist between cumulative glucocorticoid dose and fracture risk, although this finding has not been universal [7]. The risk of fracture increases rapidly in the first 3 to 6 months after glucocorticoid therapy is initiated and decreases after treatment is stopped [3,7].

The effects of inhaled glucocorticoids on bone are less certain but are potentially of great importance given their high level of use in the population. Cross-sectional data indicate that adverse effects on bone mineral density may occur, particularly when high doses are administered long-term [8–10]. In both adults and children, a small increase in relative risk of fracture has been demonstrated with inhaled glucocorticoid use, but because similar increases are seen in those using only bronchodilators, the underlying illness rather than the glucocorticoids per se is likely responsible for the observed increase [11,12].

Awareness among Healthcare Professionals

Recent studies suggest that although awareness has improved, the prevention and treatment of glucocorticoid-induced osteoporosis remains suboptimal. Curtis et al. [13] assessed changes in prevention from 1995 to 1998 and 2001 to 2003 using databases from a managed care organization. During the later period, the frequency of bone mineral density (BMD) assessment increased threefold and the use of medication twofold. However, the overall rates of screening and treatment remained relatively low, especially in men, African Americans, and individuals treated by some specialist groups.

In another study, patterns of management in individuals receiving oral glucocorticoids were examined in a large U.S. health maintenance organization [14]. Only approximately 10% received BMD assessment and 15% received treatment with bone protective medications other than hormone replacement therapy. There is also evidence that patients treated with glucocorticoids receive inadequate counseling about lifestyle measures to improve bone health. Thus, Blalock et al. [15] found that when questioned by telephone interview or written questionnaire, only one-third of patients reported that they had received advice about bone protection, and although about one half were receiving adequate amounts of calcium, only about one-third were taking the recommended dose of vitamin D. Furthermore, only one-third of patients had undergone bone densitometry in the past year.

Collectively, these studies indicate that awareness of glucocorticoid-induced osteoporosis remains relatively poor with adverse consequences on its management in clinical practice. Nevertheless, a recent study indicates the potential for improvement with organized care programs incorporating identification of patients at risk, education, care pathway implementation, and audit of outcomes [16•]. After 1 year of this program, patients' knowledge levels had improved significantly as had vitamin D status and levels of physical activity. Of those identified as high risk for fracture, 91% were receiving bone protective treatment, and significant increases in BMD in the spine and hip were demonstrated. Hence, the implementation of structured care programs has been shown to improve outcomes in glucocorticoid-treated patients. Fracture risk reduction was not demonstrated in this relatively short study but would be expected, given the high rates of treatment in high-risk individuals.

Assessment of Fracture Risk in Patients Receiving Glucocorticoids

Many risk factors for fracture have been identified in prospective population-based studies of mainly but not exclusively postmenopausal women. These risk factors include older age, female gender, Caucasian race, low BMD, low body mass index, previous history of fragility fracture, family history of hip fracture, recurrent falls, and some disease states (eg, rheumatoid arthritis) [17]. Although the role of these risk factors in predicting fracture in individuals treated with glucocorticoids has not been well studied, it is generally assumed that their effect is similar to that seen in untreated individuals. Some of these risk factors (eg, previous fracture, family history, and age) are to some extent independent of BMD and thus improve the prediction of fracture risk offered by BMD alone.

The mechanisms by which glucocorticoids increase fracture risk are complex and only partially understood. Bone loss and reduction in BMD certainly contribute, but a component of the increased fracture risk is independent of BMD and may be mediated via changes in the composition of the bone mineral/matrix composite or some other aspect of bone quality. In addition, glucocorticoid therapy may lead to muscle weakness and hence increase the risk of falls. Finally, many of the disease states for which glucocorticoid therapy is given may have independent effects on fracture risk as a result of effects on mobility, body weight, and proinflammatory cytokines.

The relationship between glucocorticoid use and fracture risk has recently been investigated in a meta-analysis of data from seven large population-based cohort studies, in which approximately 42,000 men and women were included [18••]. After adjustment for BMD, previous or current use of oral glucocorticoids was associated with a significantly increased risk of fracture, including hip fracture. This increase in risk was slightly more marked in younger than older postmenopausal women and was independent of previous fracture history. Because this analysis included past and present oral glucocorticoid use, the documented increases in relative risk of fracture are likely to underestimate the increases seen with present use.

The available data in individuals treated with glucocorticoid-induced osteoporosis have confirmed the importance of age and female gender as risk factors for fracture [3] and also indicate a relationship between glucocorticoid dose and the magnitude of increase in risk [6]. In addition, evidence exists for an independent contribution of conditions such as rheumatoid arthritis, chronic obstructive pulmonary disease, asthma, and inflammatory bowel disease. BMD assessment forms an important part of risk assessment, although the relationship between BMD and fracture risk in individuals treated with glucocorticoids remains to be defined accurately. In general, the available evidence indicates that fracture occurs at a higher BMD in glucocorticoid-treated individuals than, for example, in postmenopausal women with osteoporosis, and this finding is reflected in current guidelines. Most of the bone densitometric data in glucocorticoid-induced osteoporosis are derived from dual energy X-ray absorptiometry (DXA) measurements in the spine and proximal femur, and the role of peripheral measurements using either DXA or ultrasound has not been established. Similarly, the value of biochemical markers in fracture risk assessment in this patient group is unknown.

Prevention and Treatment of Glucocorticoid-induced Osteoporosis

General considerations

In the context of glucocorticoid-induced osteoporosis, the term primary prevention is used to denote initiation of bone protective therapy at the time glucocorticoids are initiated, whereas secondary prevention implies that bone protection is started later in the course of glucocorticoid therapy. This distinction is important because of the rapid onset of bone loss and increase in fracture risk after glu-

cocorticoid initiation, providing a strong rationale for early intervention in high-risk individuals.

Although a number of interventions have been evaluated in the prevention and treatment of glucocorticoid-induced osteoporosis, the evidence base is much less robust than that which exists in postmenopausal women. Many of the studies have been small, their designs have been suboptimal, and none have been adequately powered to show a reduction in fractures. Secondly, the timing of intervention with respect to the duration of glucocorticoid therapy, the dose of glucocorticoids used, the cumulative dose prior to intervention, and the densitometric criteria for inclusion vary considerably between trials. Thirdly, patient populations in trials differ with respect to their underlying disease, and some conditions (eg, inflammatory bowel disease) have been under-represented.

Lifestyle measures

Although the effects of lifestyle interventions or modifications on bone loss and fracture risk in patients treated with glucocorticoids have not been well documented, certain measures may be recommended. The dose of glucocorticoids should be kept to a minimum, and where possible, alternative routes of administration (eg, inhaled or topical) should be considered. Alternative formulations such as budesonide may also be considered, and other immunosuppressive agents (eg, azathioprine, methotrexate) and biologics (eg, anti-tumor necrosis factor-α antibodies, may allow reduction of the dose of glucocorticoids. A dietary calcium intake of approximately 1 g daily, good nutrition, and maintenance of a normal body weight should be encouraged. Alcohol abuse and tobacco smoking should be avoided. Finally, falls risk assessment should be undertaken when appropriate, and measures should be taken to reduce the risk of further falls.

Pharmacologic interventions

Because fracture reduction has not been a primary endpoint in any of the intervention studies in glucocorticoid-induced osteoporosis, evidence for antifracture efficacy has to be derived from post-hoc analyses or safety data. Furthermore, such evidence is restricted to vertebral fractures since the number of nonvertebral fractures in treatment studies is inadequate to sustain conclusions about efficacy at these sites. Table 1 summarizes the effects of different interventions on BMD in the spine and proximal femur and on vertebral fracture rate. It should also be noted that studies in individuals undergoing solid organ transplantation have been included in the evidence base from which this table is derived.

Table 1. Effect of pharmacologic interventions on glucocorticoid-induced bone loss and vertebral fracture: grade of recommendation

Intervention	Spine BMD	Proximal femur BMD	Vertebral fracture
Alendronate	A	A	A†
Alfacalcidol	A	A*	NAE
Calcitonin	A*	A*	NAE
Calcitriol	A*	A*	NAE
Calcium plus vitamin D	A*	A*	NAE
Clodronate	A	A	NAE
Cyclic etidronate	A	A	A†
HRT	A	A	NAE
Pamidronate	A	A	NAE
PTH	A	A	NAE
Raloxifene	No data	No data	No data
Risedronate	A	A	A†

* Inconsistent data.
† Not a primary endpoint.
A indicates evidence from at least one randomized controlled trial and/or meta-analysis of randomized controlled trials. BMD—bone mineral density; HRT—hormone replacement therapy; NAE—not adequately assessed; PTH—parathyroid hormone.

Bisphosphonates

The bisphosphonates have been most widely assessed in the prevention and treatment of glucocorticoid-induced osteoporosis, and in most European countries and in North America, they constitute the only drug class approved for this indication. Specifically, cyclic etidronate (in Europe and Canada only), risedronate, and alendronate are licensed for glucocorticoid-induced osteoporosis. Ibandronate, which is now approved for postmenopausal osteoporosis, does not have a license for glucocorticoid-induced osteoporosis.

A recent Cochrane review of the effects of bisphosphonates in the prevention and treatment of glucocorticoid-induced osteoporosis concluded that there were significant treatment benefits on lumbar spine and proximal femur BMD, but that although there was a 24% reduction in odds of spinal fractures (OR 0.76, 95% CI 0.37–1.53), this result was not statistically significant [19]. However, in subgroup analyses, significant vertebral fracture reduction has been shown for alendronate after 24 months [20] and for etidronate [21] and risedronate [22] after 12 months. Notwithstanding the potential problems associated with subgroup analyses, these data and the demonstrated beneficial effects on BMD, provide support for antifracture efficacy of these agents in the context of glucocorticoid-induced osteoporosis.

Other evaluated bisphosphonates include clodronate, ibandronate, and pamidronate [23,24]. Overall, the available evidence indicates significant treatment benefits on BMD, but no robust fracture data are available. Although not approved for the indication, intravenous pamidronate or ibandronate provide a useful option in patients who are unable to tolerate or cannot absorb oral bisphosphonates. In one study in which glucocorticoid-treated patients were randomized to either alfacalcidol plus calcium or

Table 2. Comparison of ACR and RCP guidelines for the management of glucocorticoid-induced osteoporosis

	ACR	RCP
Minimum dose/duration	5 mg/d for ≥ 6 months	Any dose for ≥ 3 months
Calcium and vitamin D	All patients	As adjunct to bisphosphonates and in individuals with evidence of deficiency
Primary prevention	All patients	Men and women ≥ 65 years old or older; previous fragility fracture
BMD measurement	All patients	Those not offered primary prevention
T-score threshold for intervention	-1	-1.5

ACR—American College of Rheumatology; RCP—Royal College of Physicians of London.

ibandronate plus calcium, greater increases in lumbar spine and hip BMD were reported in the latter group relative to baseline after 3 years' treatment [25]. In addition, a significant reduction was seen in the number of patients with new vertebral fractures in the ibandronate group compared to those taking alfacalcidol (8.6% vs 22.8% respectively, $P = 0.043$). New fractures were a secondary endpoint of this study and the number of vertebral fractures was small (5 vs 13).

Calcitonin

Studies of the effects of calcitonin on glucocorticoid-induced bone loss have produced conflicting results. The results of a Cochrane review indicated beneficial effects on bone loss at the spine and forearm but not at the proximal femur [26]. No significant effects on vertebral or nonvertebral fractures could be demonstrated.

Parathyroid hormone

Substantial increases in BMD at the spine in glucocorticoid-treated women already taking hormone replacement therapy have been reported [27]. Although no significant change in hip BMD was seen in the first year of treatment, change was observed during the second year at the total hip [28]. No fracture data are available, and currently parathyroid hormone peptides are not approved for prevention or treatment of glucocorticoid-induced osteoporosis.

Calcium and vitamin D

Studies of the effects of calcium and vitamin D have not universally shown beneficial effects, although the dose of each has varied considerably between trials. A recent Cochrane review concluded that calcium and vitamin D supplements produce a clinically and statistically significant effect on bone loss in the spine and forearm in individuals treated with glucocorticoids [29]. Evidence for a similar effect on bone loss in the hip is lacking, and no fracture data are available.

Calcitriol

Beneficial effects of calcitriol, 0.5 to 1 μg daily, on BMD, mainly in the spine, have been demonstrated in some studies [30–33], although this finding has not been universal [34,35]. No effect of calcitriol on fracture has been demonstrated in glucocorticoid-treated individuals.

Alfacalcidol

Alfacalcidol, 0.25 to 1 μg daily, has been shown to prevent bone loss from the lumbar spine and in some studies from the radius and hip [36–38]. Although there was a trend for a reduction in vertebral and nonvertebral fractures after 2 years treatment in a study in which alfacalcidol plus calcium was compared with vitamin D plus calcium, this change was not statistically significant for either type of fracture. Subsequently, significant reductions in both vertebral and nonvertebral fractures were reported after a total of 3 years treatment in the alfacalcidol group [39]. Two studies have compared the effects of alfacalcidol and alendronate in the prevention of glucocorticoid-induced bone loss [40,41]. In both of these, significantly greater beneficial effects on lumbar spine BMD were reported for alendronate than for alfacalcidol.

Current Guidelines for the Management of Glucocorticoid-induced Osteoporosis

The management of glucocorticoid-induced osteoporosis has been addressed in several national guidelines [42–47]. In 2001, the American College of Rheumatology (ACR) produced an update on its recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis, which were first published in November 1996 [42]. In the following year in the United Kingdom, a working group from the Bone and Tooth Society of Great Britain, the National Osteoporosis Society, and the Royal College of Physicians in London also produced guidelines on this topic [43].

Both sets of guidelines address prevention of bone loss in adults taking continuous oral glucocorticoids. The use of intermittent glucocorticoid therapy is discussed in the U.K. guidelines but is not covered by the management algorithm because of the lack of a sufficient evidence base. In the case of inhaled glucocorticoids, the U.K. guidelines briefly review the evidence that long-term use, particularly with high doses, may be associated with increased bone loss. However, evidence that inhaled glucocorticoid use is associated with increased fracture risk per se is currently lacking [11,12]. Neither of the guidelines includes management of children treated with glucocorticoids.

Both sets of guidelines recognize the importance of primary prevention of glucocorticoid-induced osteoporosis, although there are some differences in approach (Table 2).

Thus, the U.K. guidelines advocate primary prevention in all men and women aged 65 years and in all those with a previous history of fragility fracture, whereas the ACR recommendations advise primary prevention in all individuals starting oral glucocorticoid therapy. The U.K. recommendations apply to those committed to or likely to take oral glucocorticoids continuously for a minimum of 3 months, whereas the minimum period for the ACR guidelines is 6 months. In addition, the U.K. guidelines do not state a "threshold" dose, but the ACR recommendations apply only to those taking an oral dose of 5 mg or more of prednisolone (or equivalent).

The ACR recommends that bone densitometry is performed in all glucocorticoid-treated individuals at baseline and is repeated thereafter at appropriate intervals in order to monitor therapy. In contrast, the U.K. guidelines state that bone densitometry is not required before primary prevention is instituted, but should be used to select individuals for secondary prevention. The T-score threshold at which intervention should be considered is -1 in the ACR guidelines and -1.5 in the U.K. guidelines. Finally, universal calcium and vitamin D supplementation is recommended by the ACR, whereas the U.K. guidelines stipulate that calcium and vitamin D supplements should be used as an adjunct to bisphosphonate therapy and in other glucocorticoid-treated individuals in whom there is evidence of inadequate dietary calcium intake and/or vitamin D deficiency.

These differences between the two sets of guidelines partly reflect the lack of a robust evidence base for many aspects of the management of glucocorticoid-induced osteoporosis, but they also arise from differences in healthcare resources and in particular the availability of bone densitometry. Access to bone densitometry is not available in all parts of the United Kingdom, and where present, waiting lists are sometimes long; therefore, the recommendation that primary prevention should be instituted without the need for bone densitometry is largely driven by the rapid onset of fracture after starting glucocorticoid therapy. The more liberal approach to primary prevention exercised by the ACR will undoubtedly result in unnecessary treatment for some, whereas the restriction of primary prevention in the U.K. guidelines to older individuals and those with a previous history of fracture excludes some individuals who may be at high risk, particularly those on high doses of prednisolone. Finally, with respect to calcium and vitamin D supplementation, the U.K. approach reduces treatment costs and more importantly minimizes the number of medications in a population often already taking multiple medications. However, it can also be argued that assessment of calcium and vitamin D status in clinical practice is empirical and that advice about supplementation may therefore not always be appropriate.

Notwithstanding the differences in emphasis between the U.K. and ACR guidelines, there is consensus on the importance of primary prevention, the place of bisphosphonates as front-line treatment options, and the need for calcium and vitamin D supplementation in the majority of individuals. These seminal principles are reflected in recent reviews on the topic [5,48•]. The role of biochemical markers and bone densitometry in the monitoring of treatment in glucocorticoid-induced osteoporosis is uncertain, but measurement of spine BMD by DXA currently provides the most plausible approach. Finally, an important challenge for the future is to improve compliance and persistence with therapy; in one study, overall persistence rates were shown to be suboptimal [49•]. Younger age, greater medical comorbidity, and lack of BMD measurements were significantly associated with bisphosphonate therapy discontinuation in glucocorticoid users.

Conclusions

Growing awareness exists of the importance of glucocorticoid-induced osteoporosis in clinical practice, although further education of health professionals is required. Epidemiologic studies have greatly enhanced our knowledge of the condition and have informed management strategies. Implementation of evidence-based guidelines has the potential significantly to improve the prevention and treatment of this common and disabling complication of glucocorticoid therapy.

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