

ABSTRACT

Glucocorticoid-induced osteoporosis is the most frequent cause of secondary osteoporosis. Glucocorticoids cause a rapid bone loss in the first few months of use, but the most important effect of the drug is suppression of bone formation. The administration of oral glucocorticoid is associated with an increased risk of fractures at the spine and hip. The risk is related to the dose, but even small doses can increase the risk. Patients on glucocorticoid therapy lose more trabecular than cortical bone and the fractures are more frequent at the spine than at the hip. Calcium, vitamin D and activated forms of vitamin D can prevent bone loss and antiresorptive agents are effective for prevention and treatment of bone loss and to decrease fracture risk. Despite the known effects of glucocorticoids on bone, only a few patients are advised to take preventive measures and treat glucocorticoid-induced osteoporosis. (**Arq Bras Endocrinol Metab 2006;50/4:793-801**)

Keywords: Epidemiology; Fractures/risk factors; Glucocorticoid/adverse reactions; Osteoporosis; Review

RESUMO

Osteoporose Induzida por Glicocorticóide.

A osteoporose induzida por glicocorticóides é a causa mais freqüente de osteoporose secundária. Os glicocorticóides causam uma perda óssea rápida nos primeiros meses de uso da medicação; entretanto, o seu efeito mais importante é uma supressão significativa da formação óssea. A administração oral de glicocorticóides está associada a um aumento no risco de fraturas na coluna e no quadril. O risco é dose dependente; entretanto, mesmo doses baixas de glicocorticóides podem aumentar o risco de fraturas. Os pacientes em uso de glicocorticóides perdem mais osso trabecular que osso cortical; em conseqüência, as fraturas são mais freqüentes na coluna que no quadril. O uso concomitante de cálcio e vitamina D ou formas ativas da vitamina D previne a perda óssea, e as drogas anti-reabsorptivas são efetivas na prevenção e tratamento da perda óssea e diminuem o risco de fraturas. Apesar de os efeitos deletérios dos glicocorticóides sobre o osso serem bastante conhecidos, poucos pacientes são orientados ou recebem tratamento preventivo associado à terapia com glicocorticóides. (**Arq Bras Endocrinol Metab 2006;50/4:793-801**)

Descritores: Fraturas; Fatores de risco; Glicocorticóides; Reações adversas; Osteoporose

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FOR ABOUT 70 YEARS, Harvey Cushing described the syndrome of hypercortisolism and the associated bone loss (1932). In 1954 the effects of exogenous glucocorticoids on bone were recognized. The Cushing syndrome is relatively uncommon, but nowadays glucocorticoids are widely used in several specialties to treat a number of allergic and chronic noninfectious inflammatory disorders, chronic lung diseases such as asthma, rheumatoid arthritis and other connective tissue diseases. In spite of its wide use, the negative impact on bone mass remains its most important limitation. The administration of oral glucocorticoid is associated with a significant increase in fracture risk at the hip and spine (1). The degree of bone loss is related to the dose and duration of therapy, although prolonged exposure to a modest dose, frequently considered physiological dose of glucocorticoids, results in an increased risk of fractures (2). The fracture risk increases rapidly after the onset of treatment and declines rapidly after stopping therapy. After initiation of corticosteroid therapy, there is a phase of rapid bone loss, followed by a slower, but continuous, decline in bone mineral density (BMD). Patients exposed to high doses of glucocorticoids have decreased BMD, and 30–50% develops vertebral fractures (3). Several studies, however, show that most of the patients treated with glucocorticoids do not receive treatment to prevent bone loss (4,5). Postmenopausal women are at greater risk to develop osteoporosis after glucocorticoid exposure, although the disease also affects men and children.

Glucocorticoid therapy can enhance bone resorption, but the most important effect of glucocorticoid is suppression of bone formation through several mechanisms (6–8). Glucocorticoids decrease gastrointestinal calcium absorption and increase renal calcium excretion, which may result in modest elevations in serum levels of Parathyroid Hormone (PTH) that cannot explain all skeletal changes observed in glucocorticoid-induced osteoporosis (GIO). In men, glucocorticoids can inhibit testosterone production due to direct effects on the testis and indirect effects via suppression of gonadotropin hormone secretion. Low serum testosterone levels can contribute to the decrease of osteoblastic activation.

Glucocorticoid-induced bone loss should be prevented, and if present, should be treated. Supplementation with calcium and vitamin D, or an activated form of vitamin D should be offered to all patients receiving glucocorticoid. Antiresorptive agents are effective in prevention and treatment of GIO. Bisphosphonates also reduce the incidence of radiographic

vertebral fractures in postmenopausal women with GIO. Bisphosphonates are recommended for postmenopausal women who will initiate glucocorticoid therapy (table 1), as well as in men and premenopausal women. The therapy should be continued throughout the duration of glucocorticoid use. The use of PTH(1–34) increases BMD at the spine (9) and the vertebral cross-sectional area on postmenopausal women on corticosteroid therapy (10), which may permit speculation that PTH could be responsible for a decrease in fracture risk.

Despite the increased risk of bone loss and fractures in patients on glucocorticoid therapy, most physicians are not aware of prevention and treatment of GIO.

EPIDEMIOLOGY

GIO is the most common cause of secondary osteoporosis. Epidemiological data are difficult to obtain, because of the great variability of dose prescriptions and because of the impact of the baseline disease on the bone. In the UK, Van Staa et al. (3) developed a pharmacological recording system (General Practice Research Database — GPRD) and identified 1.6 million oral glucocorticoid prescriptions over a 10-year period. This database shows that the prevalence of oral glucocorticoid use was 0.9% of the total adult population at any age and rises to 2.5% at age 70–79. The prevalence was similar in men and women. The most frequent indication for oral glucocorticoid therapy was respiratory disease (40%), musculoskeletal and cutaneous disease.

A meta-analysis study (1) demonstrated a strong correlation between cumulative dose and loss of bone mineral density as well as between daily dose and risk of fracture. The risk of fracture increases rapidly after 3 to 6 months of the onset of glucocorticoid use and decreases after stopping therapy. This study reviewed 66 papers with BMD measurement and 23 papers that evaluated fractures. The most frequent indications for corticosteroid therapy were musculoskeletal disorders (67.1%) and obstructive pulmonary disease (15.7%). The General Practice Research Database study (GPRD) was the largest study that evaluated fractures and was analyzed separately from the other studies. The relative rate of fracture in corticosteroid users was 1.33 in the GPRD study and 1.91 in all other studies. The risk of hip fractures was 1.61 in the GPRD study and 2.01 in the other studies. The risk of vertebral fractures was 2.60 and 2.86 respectively. Spine and hip

Table 1. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis (39).**Patient beginning therapy with glucocorticoid with plans for treatment duration \geq 3 months(1)**

- Modify lifestyle risk factors for osteoporosis
 - Smoking cessation or avoidance
 - Reduction of alcohol consumption if excessive
- Instruct in weight-bearing physical exercise
- Initiate calcium supplementation
- Initiate supplementation with vitamin D (plain or activated form)
- Prescribe bisphosphonate (use with caution in premenopausal women)

Patient receiving long-term glucocorticoid(1)

- Modify lifestyle risk factors for osteoporosis
 - Smoking cessation or avoidance
 - Reduction of alcohol consumption if excessive
- Instruct in weight-bearing physical exercise
- Initiate calcium supplementation
- Initiate supplementation with vitamin D (plain or activated form)
- Prescribe treatment to replace gonadal sex hormones if deficient or otherwise clinically indicated
- Measure bone mineral density (BMD) at lumbar spine and/or hip
 - If BMD is not normal (i.e., T-score below -1):
 - Prescribe bisphosphonate (use with caution in premenopausal women)
 - Consider calcitonin as second-line agent if patient has contraindication to or does not tolerate bisphosphonate therapy
 - If BMD is normal, follow up and repeat BMD measurement either annually or biannually.

(1) In a dose of prednisone \geq 5 mg/dia or equivalent.

BMD were lower in glucocorticoid users than in the control group. In all studies the bone loss was greater in trabecular bone than in cortical bone. Long duration and continuous pattern of glucocorticoid use demonstrated a significant 5-fold increased risk of hip and 5.9-fold increased risk of vertebral fracture. The combined effect of higher dose, longer duration and continuous pattern further increased the risk to 7-fold for hip and 17-fold for vertebral fractures (11). There is a strong correlation between daily dose and risk of fracture, as observed in GPRD study — the higher the dose, the higher the risk, and only a weak correlation between cumulative dose and risk of fracture (12). The hip fracture risk in the GPRD study is 1.77 at daily doses of 2.5 to 7.5 mg and 2.27 at daily doses of 7.5 mg or greater. For vertebral fractures, the risk is 1.55 for daily doses of less than 2.5 mg, and increases to 2.59 and 5.18 at daily doses of 2.5 to 7.5 mg and doses of 7.5 mg or greater, respectively (3). Patients who took cumulative doses of less than 0.5 g prednisolone experienced a non-vertebral fracture risk of 1.8, while those who had consumed a total of 10 g prednisolone or more had a risk of 2.7 (12). Other studies observed positive correlations between cumulative dose and fracture risk (13,14). Otherwise, there is a strong correlation between cumulative dose and decreases in

spine and hip BMD. In the GPRD study the risk of non-vertebral fractures in patients using 7.5 mg, or more, prednisolone per day, increased by 54% in the first year of glucocorticoid therapy. The risk of vertebral fractures is also increased in the high-dose group. The risk of new vertebral fractures within the first year of therapy is higher than that observed before initiating therapy, as observed in other trials. The rate of bone loss is rapid during the first months of therapy and slows down after one year of therapy. There is strong evidence to suggest that increased risk of fracture is reversible after stopping therapy. In the GPRD study this effect is more pronounced for vertebral fractures than for hip fractures (3) and for previous higher exposure (12). Longitudinal studies found substantial increases in BMD after discontinuation of glucocorticoid therapy (15) and patients with Cushing syndrome showed normal BMD after the cure of the disease (16).

The results are conflicting with respect to the influence of sex, age and underlying disease on fracture risk and BMD, but it seems that they have a minor influence on BMD in patients on glucocorticoid therapy. In several studies with patients with the same disease the lumbar spine BMD was 3.6% lower in glucocorticoid users than in non users and the hip BMD was 6.2% lower in glucocorticoid users, suggesting

that most of bone loss is related to glucocorticoid therapy. The rate of vertebral fractures is higher in glucocorticoid users than in idiopathic osteoporosis (17) or postmenopausal osteoporosis (18), even with similar levels of BMD, which can be attributed to the deleterious effects of glucocorticoid on bone microarchitecture. The most common effect on architecture is trabecular thinning rather than perforation or disconnection of trabecula as in idiopathic osteoporosis (19). Inhaled corticosteroid therapy is also associated with bone loss (20). The skeletal effects of inhaled glucocorticoids appear to depend on both dose and the duration of use. Other studies, however, showed an increased risk of fracture, but this risk was associated with the underlying respiratory disease rather than inhaled corticosteroid (21).

MECHANISMS OF GLUCOCORTICOID ACTION ON BONE

Glucocorticoids may exert their effects on the skeleton in many ways. Although there is an earlier increase in bone resorption, it is now apparent that the most important effect of glucocorticoids in GIO is their action in decreasing bone formation. There are glucocorticoid receptors in bone cells. Glucocorticoids affect the differentiation and activity of osteoblast lineage cells, the transcription of many of the genes responsible for the synthesis of matrix constituents by osteoblasts such as type 1 collagen, osteocalcin, fibronectin, alkaline phosphatase and others, and the synthesis and activity of many locally acting factors, including cytokines (interleukins 1 and 6), insulin-like growth factors (IGF-I and IGF-II) and several IGF-binding proteins (IGFBP-3, 4 and 5). Recent evidence indicates that besides the decrease in osteoblastogenesis, there is an increase in the apoptosis of mature osteoblasts and osteocytes (22). Glucocorticoids also act on osteoclastogenesis through osteoblastic signals on the receptor activator of the nuclear factor κ B ligand (RANK-L) — osteoprotegerin (OPG) axis. Glucocorticoids enhance RANK-L, which binds and activates RANK on the surface of osteoclast precursor, and also inhibit OPG production, with a consequent induction of osteoclastogenesis (8) and an early increase in bone resorption in GIO. This increased bone resorption can explain the response to antiresorbing drugs in the management of GIO.

Glucocorticoids inhibit calcium absorption in the gastrointestinal tract and induce renal calcium loss, but do not appear to cause secondary hyperparathy-

roidism. Several studies found an increase in PTH levels and urinary calcium excretion. One of them suggests that a vitamin D deficiency (23) can contribute to the reduction in calcium absorption and elevated PTH secretion. A direct effect of glucocorticoid on the glandular secretion of PTH can also contribute to the elevated PTH serum levels (24). Other data indicate that PTH levels are not changed in patients using glucocorticoids (25). Rubin and Bilezikian (26) reviewed the role of PTH in GIO and primary hyperparathyroidism by analyzing dynamic studies, densitometric studies and histomorphometric studies and concluded that the differences in the action of PTH on those conditions support that PTH is not involved in the pathogenesis of GIO. Chronic glucocorticoid treatment reduces the amount of tonical release of PTH and increases the amount of pulsatile secretion. Densitometric studies do not support the involvement of PTH in the mechanisms of bone loss in patients using glucocorticoids. The reduction in lumbar spine BMD is significantly higher than the reduction in distal radius. Studies using QCT show a greater decrease in trabecular bone than cortical bone in GIO (27), in contrast to the cortical bone loss observed in primary hyperparathyroidism. Another study, however, showed that BMD of the radius by pQCT appears to be more useful to predict new vertebral fractures than trabecular BMD (28). Histomorphometric studies also suggest that PTH plays a minor role in bone loss in GIO. There is a decrease in trabecular thickness and in cancellous bone volume whereas a different picture is observed in primary hyperparathyroidism where there is a cortical thinning with maintenance of cancellous bone volume (29). We can also observe a reduction in trabecular connectivity in GIO (30) as opposed to the maintenance of trabecular microarchitecture in primary hyperparathyroidism (31). Several other histomorphometric parameters are different in GIO and primary hyperparathyroidism (26). We also observe a reduction of gonadal hormones through an inhibitory effect of glucocorticoid on the pituitary gonadotropins, decreasing LH and FSH production and reducing gonadal sex steroid production.

CLINICAL FEATURES

Patients with GIO lose more trabecular than cortical bone, so they have a greater risk of bone loss in spine than in the hip. There is an initial rapid bone loss followed by a stabilization of BMD, but these patients continue to have a greater risk of fracture and there-

fore require aggressive therapy. A recent study (32) revealed that high doses of glucocorticoid (≥ 40 mg/daily prednisolone or equivalent) for only 2 months resulted in substantial BMD loss, most markedly in the lumbar spine, followed by femoral neck and total body. A decrease in lean body mass (LBM) was also observed, which could also be responsible for the increased risk of fracture, since it can lead to an increased risk of falls. Moderate doses of inhaled corticosteroids seem to carry less risk than oral therapy in postmenopausal women (33). Children using inhaled corticosteroids are at increased risk for fracture. This increased risk is more likely to be the result of the underlying disease than the usage of inhaled corticosteroids (34). Whenever possible, inhaled corticosteroids should be used due to their less negative impact on bone loss.

Postmenopausal women are at greater risk to develop osteoporosis after glucocorticoid exposure, although the pathogenesis in male and female is similar and the therapeutic approaches for women should be the same for men. Patients who underwent kidney, liver, heart and lung transplants and are using glucocorticoid and other immunosuppressive agents are at greater risk of bone loss, although hypogonadism, vitamin D deficiency, malnutrition and reduced physical activity are involved in the pathogenesis of osteoporosis after organ transplants (35). Fracture incidence is highest in the first year after transplantation. Patients with rheumatoid arthritis develop osteoporosis more evident at the hip and the radius than at the spine, and patients in corticosteroid therapy have lower BMD than untreated patients. Patients with Systemic Lupus Erythematosus (SLE) presented bone loss secondary to the disease itself and the agents used in its treatment (36). Patients with asthma, chronic lung disease and sarcoidosis treated with corticosteroids develop osteoporosis (3,21). Although clinical risk factors such as age, sex, race, history of previous fracture and family history of fractures have not been evaluated in patients using glucocorticoids, it is important to consider those clinical factors in the assessment of fracture risk in glucocorticoid-induced osteoporosis.

DIAGNOSTIC EVALUATION

Bone mineral density

Bone loss resulting from glucocorticoid is usually most marked in trabecular bone. Declines of up to 8% of lumbar spine bone mineral density within 20 weeks have been detected by dual energy X-ray absorptiometry (DXA) (37).

Recent study suggested that the risk of vertebral fractures is greater in patients using glucocorticoids at the same BMD or even higher BMD than in non users and showed a higher prevalence of vertebral fractures in glucocorticoid users, despite a higher mean lumbar spine BMD (17). In contrast, Selby et al. (38) found a similar frequency of vertebral fractures and bone mass in users and non users of glucocorticoid therapy, suggesting that glucocorticoids do not alter the fracture threshold. Despite conflicting results, it appears that a higher BMD threshold should be used for estimating fracture risk in patients on glucocorticoids. BMD measured by DXA may be used for monitoring response to therapy. Because of rapid bone loss and rapid bone formation after treatment, monitoring is recommended every 6 or 12 months (39). The Committee of American College of Rheumatology (39) recommends a BMD test at the lumbar spine and/or hip when the patient will initiate long-term (> 6 months) glucocorticoid therapy. The BMD test may be repeated every 6 months for monitoring glucocorticoid treated patients to detect bone loss. In patients receiving therapy to prevent bone loss, a one-year follow-up measurement is sufficient.

Considering that fractures occur at a higher BMD level in GIO than in postmenopausal osteoporosis, it is recommended the use of a T-score cut-off of -1.5 SD as an indication for treatment in UK consensus and a T-score cut-off of -1.0 SD in the American College of Rheumatology Recommendations (39). Peripheral technologies to measure bone density are not recommended. Quantitative ultrasound (QUS) and Quantitative Computed Tomography (QCT) can detect low bone mass. There are no prospective data, however, showing the ability of these techniques to predict fracture risk and monitor changes in bone density. Lane et al. (9) demonstrated that QCT has a greater sensitivity to detect the effects of bone forming agents. They observed after 1 year of treatment with PTH, an 11% increase in BMD by DXA and a 33% increase in volumetric bone density by QCT. More research is needed on these other techniques before they can be recommended for use in patients with GIO.

Biochemical markers

The decreased osteoblastic activity may be assessed by measuring the serum levels of osteocalcin, total alkaline phosphatase, bone specific alkaline phosphatase and procollagen type I carboxi-propeptide (40,41). Changes in bone resorption markers are not yet well explained in patients using glucocorticoids. Serum

osteocalcin levels are decreased in eumenorrheic patients with Cushing Syndrome and urinary hydroxyproline and free deoxypyridinoline excretion are elevated, denoting increased bone resorption (42). In patients with multiple sclerosis who took a high-dose, short-term glucocorticoid therapy, an immediate and significant fall of osteocalcin and propeptide of type I collagen (PINP) was found, which persisted throughout the whole treatment period. Bone alkaline phosphatase showed only a modest decrease and the serum levels of CTX (C-terminal telopeptides of type I collagen) showed a progressive and marked increase during treatment with a subsequent decrease at the end of the treatment showing that corticosteroids cause a persistent decrease in bone formation and a transient increase in bone resorption (43). In patients with chronic glomerulonephritis, glucocorticoids reduced transiently serum levels of osteocalcin, bone alkaline phosphatase and osteoprotegerin and increased serum TRAP – Tartrate-resistant acid phosphatase activity, a marker of bone resorption (44). The serum concentration of bone markers was evaluated in elderly men after a short period of corticosteroid therapy. No difference was found between patients and controls for serum TRAP, whereas mean serum CTX was significantly higher in steroid treated patients. Bone alkaline phosphatase was similar between the two groups and a decrease in osteocalcin was observed in the early phase of therapy (45).

PREVENTION AND TREATMENT

Because rates of bone loss are greatest in the first few months of glucocorticoid administration, treatment for periods as short as three months may result in increased risk and thus the need for prevention of bone loss and fracture should be carefully considered in this situation. Preventive measures should also be provided for patients receiving intermittent courses of oral glucocorticoid over long periods of time, since bone loss is related to cumulative doses of glucocorticoids. Treatment should be instituted in patients already on glucocorticoid therapy and presenting low bone density particularly if fractures have already developed (table 1). Calcium and vitamin D supplementation should be provided to all patients receiving glucocorticoid therapy (39). Calcium (1,000 mg/day) and vitamin D (500–800 IU/day) maintain bone mass in patients receiving low-to-medium dose of glucocorticoid therapy (46). Similar results were noted in other studies in patients using 15-mg/day prednisone who

received 1,000 mg of calcium and 400 IU vitamin D daily (47). However, calcium and activated form of vitamin D prevent bone loss in patients receiving medium-to-high dose of glucocorticoid therapy (48). A meta-analysis and an original study (48,49) demonstrated that activated forms of vitamin D (alphacalcidol and calcitriol) are effective in preventing bone loss in patients using glucocorticoid, but the efficacy in reducing the number of fractures remains to be determined. Another meta-analysis (50) demonstrated that active vitamin D3 analogues not only preserve bone loss, but are also effective in decreasing the risk of vertebral fractures. Bisphosphonates, however, are more effective in preserving bone and decreasing the risk of vertebral fractures than vitamin D analogues.

Antiresorptive agents are effective in the treatment of GIO, as they can prevent bone loss and increase lumbar spine bone mass and maintain hip bone mass. Bisphosphonates, particularly alendronate and risedronate, have proven efficacious in the prevention and treatment of glucocorticoid-induced osteoporosis. Studies with patients receiving glucocorticoid therapy reported significant increases of BMD of the spine and femoral neck in patients using alendronate and decreases in control groups. The risk of new vertebral fractures was decreased in the treated group (51). Several studies demonstrated that bisphosphonates reduce the incidence of vertebral fractures (52,53). Risedronate preserves bone mass in postmenopausal women with rheumatoid arthritis receiving glucocorticoids while patients receiving a placebo have significant bone loss (54). Risedronate reduces vertebral fractures in patients with corticosteroid-induced osteoporosis by as much as 70% after one year of treatment and increases BMD by 2.9% at the lumbar spine and 1.8% at the femoral neck (47). Treatment with bisphosphonates is recommended to all men and postmenopausal women (receiving or not HRT) who will initiate long-term glucocorticoid treatment at a daily dose \geq 5 mg prednisone or equivalent and in men and postmenopausal women with BMD T-score below normal in the lumbar spine or in the hip. In patients receiving glucocorticoids for asthma etidronate significantly increased BMD over 5 years at the lumbar spine but not at the hip and had little effect against fractures (55).

There is literature to support the efficacy of estrogen in preventing glucocorticoid-induced bone loss and to prevent fractures in postmenopausal women. Hormone replacement therapy (HRT) should be used to prevent bone loss if not contraindicated. Raloxifene, a selective estrogen-receptor modulator,

increases bone mass and decreases vertebral fracture risk in postmenopausal women, but prospective studies are not available and little is known about its impact on GIO.

Calcitonin, subcutaneously or inhaled, increases BMD at the lumbar spine but not at the femoral neck in GIO (56,57). However, calcitonin does not reduce the risk of vertebral fracture. Calcitonin can be considered a second-line drug for treatment of low bone mass in GIO, but is not recommended for prevention of bone loss. Pamidronate 30 mg intravenous single dose at 3 months interval did not increase bone mineral density at the lumbar spine in women with steroid-induced osteoporosis (58). Three monthly intermittent i.v. ibandronate injections for two years are efficacious and well tolerated in patients on use of glucocorticoids and increases BMD at the lumbar spine and femoral neck, although no significant effect was observed in risk fracture (59,60). PTH(1-34), an anabolic agent, has been used to treat glucocorticoid-induced osteoporosis. Postmenopausal women receiving glucocorticoid therapy who were treated with PTH for 1 year presented an increase of ~11% at the lumbar spine BMD (9).

The American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis developed recommendations for clinical practice in glucocorticoid-induced osteoporosis in 1996. In 2001 these recommendations were reviewed and updated (39). In table 1 are summarized these recommendations. Despite these data showing the deleterious effect of glucocorticoid on bone, preventive medications are not widely considered in the treatment of patients taking glucocorticoids. In The GPRD study, more than 240,000 patients received continuous glucocorticoids, but only 14% were prescribed prophylaxis. In a study at San Francisco General Hospital, only 58% of 215 outpatients taking prednisolone were given prophylaxis (61). We conclude that physicians should be aware of the potential dangers of the medication and that prevention and treatment of glucocorticoid-induced osteoporosis should be prescribed to all patients receiving glucocorticoid therapy.

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