

**GLUCOCORTICOID-INDUCED OSTEOPOROSIS: RISK FACTORS, PREVENTION,
AND TREATMENT WITH RISEDRONATE**

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ABSTRACT

[to be added later]

Osteoporosis from all causes is a major health threat, affecting approximately 20 to 25 million persons in the United States (Cunnane and Lane 2000). An additional 18 million individuals have low bone mass, which places them at risk for osteoporosis. (NIH Panel, 2001) Although it was once thought to be a disease largely affecting elderly women, osteoporosis is no longer considered age- or sex-dependent. (NIH Panel, 2001)

Osteoporosis is a common complication of glucocorticoid treatment, occurring in at least 50% of patients who require long-term steroid therapy and carrying significant physical as well as financial and psychosocial consequences for affected individuals and their families and communities. (Lukert and Raisz 1990; Saag et al. 1998, 1999; NIH Consensus Development Panel, 2001) Even more alarming than the impact of the disease itself is the toll osteoporosis takes in the form of related fractures. More than 1.5 million osteoporosis-related fractures occur each year in the United States (Lukert and Raisz 1990), with an estimated treatment cost of \$10 to \$15 billion in direct financial expenditures (NIH Panel, 2001). This does not include the indirect costs of lost wages and lost productivity of the patient and caregiver, and thus these figures represent a significant underestimate of the true impact of osteoporosis in this country.

Despite the prevalence of glucocorticoid-induced osteoporosis (GIO), its treatment remains relatively neglected, and many patients receiving long-term glucocorticoid therapy receive no prophylaxis against bone loss. (Brand et al. 1999; Saag et al. 1999; Soucy et al. 2000; Valentine and Sninsky 1999; Walsh et al. 1996). The purpose of this review is to examine the mechanism of action and severity of bone loss in GIO, discuss additional risk factors for osteoporosis in diseases treated with glucocorticoids, and summarize the findings in recent studies of bisphosphonate treatment for osteoporosis, concentrating primarily on studies of risedronate, which is currently the only bisphosphonate approved for the prevention of GIO.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Glucocorticoids are used by millions of people in the United States for a wide variety of diseases and conditions. Such treatment may be lifesaving and may provide great relief of symptoms to patients, but it can also have serious side effects, one of which is osteoporosis (Baxter 2000). In fact, osteoporosis has been called the most predictable and debilitating complication of long-term glucocorticoid therapy. (Saag et al. 1998)

In general the side effects of glucocorticoid therapy are proportional to the steroid dose and duration of treatment. (Blair et al. 2000; Reid 2000; van Staa 2000) Virtually all patients who receive long-term (>6 months) glucocorticoid therapy in doses >5 mg/d lose bone, with the amount of bone loss dependent on the steroid dose. (Reid 2000; van Staa et al. 2000) Daily doses of oral prednisone ≥ 7.5 mg or more or cumulative doses >10 mg produce the most significant osteoporotic effects, and alternate-day administration does not reduce the risk. (Baxter 2000; Blair et al. 2000; Kipen et al. 1999; Morand 2000; Reid 2000; Reid et al. 2000; Soucy et al. 2000)

In some conditions it is possible to administer local steroid treatment, thereby reducing the systemic side effects. However, bone loss has also been demonstrated with the use of intranasal (Lipworth and Jackson 2000) and inhaled (Bonala et al. 2000; Lipworth 1999; Singh and Muskelly 2000; Tattersfield et al. 2001; Wong et al. 2000) steroids, though not all studies have shown this (Sorkness 1998). The evidence of the association between osteoporosis and inhaled glucocorticoids is more limited than for oral glucocorticoids (Smith et al. 1999), but it appears that decreases in bone mineral density (BMD) are related to a high daily dose of inhaled steroids, rather than the duration of the dose (Fairney 1999; Goldstein et al. 1999). **Table 1** shows the threshold dosages for inhaled glucocorticoids above which significant bone loss is thought to occur (Goldstein et al. 1999).

The usual risk factors for osteoporosis do not apply to GIO. Young patients receiving long-term steroid treatment lose bone more rapidly than do older patients and premenopausal women; however, postmenopausal women receiving equivalent doses of steroids are more at risk for fractures, possibly because of age- and menopause-related bone loss. Men are equally susceptible to the skeletal effects of glucocorticoids—surprisingly, men younger than 50 years may lose a higher percentage of bone than postmenopausal women (Blair et al. 2000)—and blacks lose bone to an equal extent as whites. (Lukert and Raisz 1990) Non-disease-specific risk factors for osteoporosis are shown in **Table 2**. (Goldstein et al. 1999)

Mechanism of Action

Glucocorticoids inhibit osteoblast formation and bone deposition. Effects may be amplified as a result of inhibition of release of growth factors such as insulin-like growth factor-1 (IGF-1) and transforming growth factor- β (TGF- β). (Baxter 2000) In addition, glucocorticoid-related effects

on excretion of calcium and inhibition of calcium absorption promote a tendency toward hypocalcemia, with secondary increases in parathyroid hormone (PTH), which appears to increase bone resorption. (Baxter 2000; Blair et al. 2000) Glucocorticoids can also promote bone loss through direct effects on the gonads and inhibition of the release of gonadotropins, thereby decreasing levels of testosterone in men and estradiol in women; however, these effects are not observed in all cases (Blair et al. 2000; Baxter 2000). Finally, muscle atrophy and subsequent wasting, perhaps the most observable consequences of glucocorticoid treatment, result in loss of the mechanical stimuli required to generate new bone formation (**Table 3**) (Blair et al. 2000)

Rate and Severity of Bone Loss

As stated earlier, the severity of bone loss is related to the dose and duration of treatment. (van Staa 2000; Reid 2000; Blair et al. 2000) Bone loss is generally greatest during the first 6 months of treatment, and an average bone loss of 5% occurs over the first year of long-term treatment (Reid 2000; Blair et al. 2000; Reid et al. 2000). Bone loss thereafter is 1% to 2% per year, although estimates vary (Baxter 2000; Blair et al. 2000). Trabecular bone (including the proximal femur) and the cortical rim of the vertebral body are more susceptible to the effects of steroids than the cortical bone of the long bones (Baxter 2000; Reid et al. 2000). Thus the lumbar spine and proximal femur are particularly vulnerable to osteoporosis and related fractures. (Baxter 2000)

The bone loss induced by glucocorticoids is substantially reversible after withdrawal of treatment. (Reid 2000) Two studies have shown that after glucocorticoid withdrawal, BMD was reversible over approximately the same time span as the loss occurred. (Laan et al. 1993; Rizzato and Montemurro 1998) Alternate-day administration of glucocorticoids, however, does not decrease bone loss. (Reid 2000)

This decrease in BMD results in an incidence of fractures that is 2 to 4 times higher in patients treated with glucocorticoids than in those who have never received such therapy. (Blair et al. 2000) Although the true incidence of osteoporotic fractures from chronic glucocorticoid use is unknown, Reid (1997) has estimated that approximately 30% of adults receiving glucocorticoids for 5 years or longer experience GIO-related fractures. Saag et al. (1998) placed the incidence much higher, at 50% over the course of treatment. Retrospective cross-sectional studies have agreed with these estimates, with results showing that 30% to 50% of patients receiving long-term glucocorticoid treatment develop fractures. (Cunnane and Lane 2000; Michel et al. 1991; Adinoff and Hollister 1997; Blair et al. 2000)

All fracture types can result in skeletal deformities that cause extreme pain, exacerbate the primary autoimmune or inflammatory disease state, and represent a significant financial burden. In addition, the estimated incidence of mortality after a hip fracture in patients receiving

long-term glucocorticoid treatment ranges from 5% to 9% in men older than 50 years and from 1% to 3% in age-matched women. (Blair et al. 2000)

BONE LOSS AND RISK FACTORS FOR OSTEOPOROSIS IN SPECIFIC DISEASE STATES

The risk of osteoporosis is increased by glucocorticoid therapy, but the underlying diseases themselves also negatively affect bone health. Thus even patients receiving only rescue or very-low-dose steroid therapy may have a greater risk for osteoporosis than previously realized. Long-term glucocorticoid treatment is used for a wide variety of disease states, including liver disorders, gastrointestinal disorders, rheumatologic disorders, adrenal insufficiency, renal diseases, and pulmonary disorders, and in post-transplant patients. These disease states and some associated additional risk factors for osteoporosis are summarized in **Table 4**.

Liver Disorders

Maintenance of optimal bone status is indicated for all patients with chronic liver disease. (Wolfhagen et al. 2000) Metabolic bone disease, primarily osteoporosis, is a well-known complication of primary biliary cirrhosis (PBC), which primarily affects elderly women, who are naturally prone to osteoporosis. Patients with PBC exhibit few signs of osteoporosis at the time of presentation, but because of their predilection to its development, it is even more important to take early measures to prevent the development of this disease. Patients with late-stage disease have significantly lower spinal body mass than patients with early-stage disease, and the duration of PBC is significantly longer in PBC patients with osteoporosis than in those without. The rate of vertebral bone loss in women with PBC is twice that in healthy women, and between 12% and 50% of all PBC patients have osteoporosis or a BMD below the fracture threshold. (Wolfhagen et al. 2000) One study found that the prevalence of skeletal fractures in patients with chronic liver disease was twice that of healthy controls matched for age, sex, and menopausal status. (Diamond et al. 1989)

Although PBC has traditionally been associated with osteoporosis, other chronic liver disorders (eg, primary sclerosing cholangitis, chronic autoimmune and viral hepatitis, hemochromatosis, and alcohol-related liver disease) are equally associated with osteoporosis. (Wolfhagen et al. 2000) The problem of osteoporosis appears to have become less serious in patients with chronic liver disease since the introduction of liver transplantation, which has reduced the overall numbers of patients with longstanding, advanced disease. However, it is even more important to prevent loss of bone mass in these patients, as bone status is severely compromised by the liver transplantation procedure itself. (Wolfhagen et al. 2000)

Gastrointestinal Disorders

Inflammatory bowel disease (IBD) (eg, Crohn's disease and ulcerative colitis) is associated with decreased BMD and an increased risk of osteoporosis. (Scharla et al. 1994) The pathophysiology is unknown but is probably a combination of several factors: the inflammatory process itself and its attendant release of cytokines may have a direct effect on bone mineralization, and bone formation may be inhibited by episodes of malabsorption and malnutrition and periods of physical inactivity during acute relapse. (Cowan et al. 1997) Bone turnover in IBD is characterized by low bone formation in the presence of normal levels of calcium-regulating hormones (Abitbol et al. 1995) but is significantly higher in patients with ulcerative colitis than in those with Crohn's disease (Ardizzone et al. 2000). In addition to these factors, IBD often necessitates treatment with relatively high doses of steroids for prolonged periods of time, placing patients at further risk of osteoporosis. (Cowan et al. 1997)

The low BMD common in patients with inflammatory bowel disease exposes them to a risk of fracture. (Pigot et al. 1992; Robinson et al. 1998) One study found that BMD was more than 2 SD below normal in 23% of patients, all of whom who had received steroid therapy, but did not differ in the 29% of patients who had never received steroids. (Pigot et al. 1992) Another study found that BMD was reduced by 11% in IBD patients compared with healthy controls. (Scharla et al. 1994)

Patients with IBD have lower serum levels of vitamin D, despite comparable levels of vitamin D intake, when compared with healthy controls. (Silvennoinen 1996) It has generally been thought that malabsorption of calcium and secondary hyperparathyroidism contribute to the lower bone mass seen in IBD patients (Kelts et al. 1979; Bjarnason et al. 1997; **CHC: Need refs. here; these refs. cite someone else, but I only have the abstract for the refs. and thus don't know what refs. they cite.**), although some studies (Scharla et al. 1994; Silvennoinen 1996) have not shown this. Major determinants of BMD in patients with Crohn's disease are body weight, current steroid use, and cumulative steroid dose. Men with Crohn's disease are at greatest risk of osteoporosis, with jejunal involvement and previous bowel resection also contributing to low BMD. (Robinson et al. 1998) Children with IBD frequently have a delayed and truncated pubertal growth spurt, which may have adverse effects on their achievement of peak bone mass. These factors in childhood may predispose these patients to osteopenia and osteoporosis and increase their risk of fracture in later adult life. (Cowan et al. 1997)

Despite the high prevalence of osteopenia or osteoporosis in patients with IBD, few patients receive prophylactic therapy for the prevention and treatment of GIO. (Valentine and Sninsky 1999).

Rheumatologic Disorders

Rheumatoid Arthritis. Although low-dose glucocorticoids have an undisputed role in the temporary (up to 1 year) relief of symptoms in rheumatoid arthritis (RA) patients, in clinical practice long-term (>1 year) use of such treatment is the rule rather than the exception. (Laan et al. 1999; Morand 2000) One study has shown that the incidence of osteoporosis in RA patients aged 20 to 70 years is twice that in similar healthy controls (Haugeberg et al. 2000) Among female RA patients taking ≥ 5 mg of prednisone daily, the 5-year probability of fracture is 34%. (Michel et al. 1991)

Rheumatoid arthritis patients are at an increased risk for osteoporosis due to disease-related release of interleukin-1 (IL-1), IL-6, and tumor necrosis factor- α (TNF- α) from synovial macrophages, fibroblasts, and T cells; this process is thought to contribute to both periarticular and generalized bone loss. (Dequeker et al. 1995; Cunnane and Lane 2000) Furthermore, the disability caused by pain and inflammation is inversely related to BMD in RA patients. (Sambrook et al. 1987). These factors are exacerbated by long-term glucocorticoid therapy.

Sex hormone status, which is an important determinant of low BMD in women, may also play a role in the pathogenesis of low BMD in RA patients. (Fiter et al. 2000) Adrenal androgens may contribute to the maintenance of bone mass after menopause, and lower levels of such androgens as dehydroepiandrosterone (DHEAS) and androstenedione (AND), which are correlated with lower femoral BMD, may be a risk factor for osteoporosis in postmenopausal RA patients. (Fiter et al. 2000; Nordin et al. 1985) However, lower DHEAS and AND levels appear to be related to the use of glucocorticoids and not to the underlying disease. (Fiter et al. 2000) Other risk factors for fracture in RA patients include duration of glucocorticoid therapy, previous diagnosis of osteoporosis, disability, age, lack of physical activity, female sex, disease duration, impaired grip strength, and low body mass. (Michel et al. 1993)

Although many rheumatology patients have multiple risk factors for osteoporosis and fracture, physicians only infrequently prescribe anti-osteoporotic medications (Brand et al. 1999; Soucy et al. 2000). Any such medications that are prescribed consist largely of hormone replacement therapy in postmenopausal women (Brand et al. 1999); thus a large proportion of RA patients are placed at even greater risk of osteoporosis and fracture.

Systemic Lupus Erythematosus. The true incidence of osteoporosis in systemic lupus erythematosus (SLE) is unknown (Cunnane and Lane 2000), but musculoskeletal damage remains one of the major sequelae of SLE (Petri 1995) Although nearly all studies performed on SLE patients show decreased bone mass at either the lumbar or femoral level, the prevalence of osteoporosis in these studies varies, largely due to small sample sizes and inclusion of patients never treated with glucocorticoids. (Sinigaglia et al. 1999) Sinigaglia and coworkers (1999) found that osteoporosis was a frequent manifestation in SLE patients, occurring in 23% of those studied.

The inflammatory process of the disease itself may negatively influence bone loss through induction of bone-resorbing mediators such as IL-1, IL-6, and TNF- α , which may alter bone metabolism and influence the development of osteoporosis. (Cunnane and Lane 2000; Sinigaglia et al. 1999) B-cell lymphokine-mediated bone resorption has also been observed in lupus patients. (Tanaka et al. 1989) Kidney damage in SLE may result in an impaired ability to manufacture calcitriol, which, over time, may lead to secondary hyperparathyroidism and increased osteoclastic bone resorption. In patients with severe renal disease, aluminum-containing agents administered to prevent phosphorus absorption from the gastrointestinal tract interfere with bone formation. Additional factors contributing to osteoporosis in these patients include acidosis, iron accumulation, and deficiencies in growth factors. (Cunnane and Lane 2000)

Bone loss and osteoporosis in SLE patients are also related to disease severity as measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for SLE (SLICC/ACR) score (Gladman et al. 1996), which can be used to identify patients with severe disease. (Sinigaglia et al. 1999; Kipen et al. 1998) Because of their extensive use, glucocorticoids are thought to be the most frequent cause of drug-related osteoporosis in SLE and may be responsible for much of the bone loss seen in SLE patients. (Cunnane and Lane 2000) One study found that steroid exposure was the only treatment-related variable that exerted an influence on the development of osteoporosis in SLE patients. (Sinigaglia et al. 1999)

Medications other than glucocorticoids may also contribute to the development of osteoporosis in SLE patients. Methotrexate, often used as steroid-sparing therapy, is linked to the development of osteoporosis, bone pain, and fractures when given in high doses. Anticonvulsants and anticoagulants used to treat the complications of SLE may also decrease BMD. (Cunnane and Lane 2000)

In addition to glucocorticoid treatment, patients with SLE have other risk factors for osteoporosis. Those with photosensitivity must avoid sunlight and may have an associated vitamin D deficiency. Joint or muscle inflammation, pain, and fatigue all contribute to poor mobility, making it difficult for these patients to participate in the weight-bearing exercise needed to maintain bone health. Estrogen, which may be involved in the pathogenesis of SLE, is also implicated in bone loss, as mouse models of SLE have shown a relatively high estrogenic and low androgenic hormonal environment. (Cunnane and Lane 2000; van Vollenhoven et al. 1994) In addition, SLE frequently appears in young persons before the achievement of peak bone mass, reducing their chance of having normal BMD. (Cunnane and Lane 2000)

The marked increase in survival rates over the past few decades has sparked interest in factors affecting long-term morbidity. (Sinigaglia et al. 1999) Two recent studies have shown that BMD is negatively correlated with cumulative glucocorticoid intake and is significantly

decreased in premenopausal SLE patients when compared with healthy age-matched controls. (Jardinet et al. 2000; Sinigaglia et al. 1999) This has important implications, since SLE predominantly affects fertile women. Because a growing number of SLE patients are expected to reach menopause, bone loss in these patients represents an additional clinical challenge. (Sinigaglia et al. 1999) Therefore, preventive osteoporosis treatment should be given to all premenopausal SLE patients who are prescribed glucocorticoids. (Jardinet et al. 2000) Two studies have shown the effectiveness of bisphosphonate treatment in preventing loss of BMD and reducing the incidence of fractures. (Boutsen et al. 1997; Saag et al. 1998)

Adrenal Insufficiency

Historically patients in need of replacement therapy for hypoadrenalism have received hydrocortisone 20 to 30 mg daily, a dosage selected because it had been shown to be equivalent to classical estimates of the daily secretion rate of cortisol. (Jeffcoate 1999) However, several researchers and at least one study support the belief that such doses are too high (Esteban et al. 1991; Zelissen et al. 1994; Florkowski et al. 1994; Peacey et al. 1997) A second difficulty is that the aim of treatment may not always be simply that of correcting glucocorticoid deficiency. Instead the goal might be suppression of nocturnal adrenal corticotropic hormone (ACTH) secretion, as in glucocorticoid management of congenital adrenal hyperplasia or polycystic ovary syndrome. Because suppression of nocturnal ACTH secretion can usually be achieved only by inducing abnormally high circulating glucocorticoid levels, it is much easier to err on the side of over- rather than undertreatment. Thus patients treated for cortisol replacement may be overtreated, with an attendant increased risk of osteoporosis. (Jeffcoate 1999)

One study found glucocorticoid dose-related decreases in BMD in patients with secondary hypoadrenalism. (Peacey et al. 1997) Such an effect in patients with hypothalamic and pituitary disease raises the question of the relative contribution to osteoporosis risk made by disease-associated hypogonadism and growth hormone deficiency, use of excessive doses of thyroxine replacement, and, most importantly, earlier glucocorticoid exposure in patients whose initial problem was Cushing's disease. (Jeffcoate 1999)

Renal Diseases

The schedule of treatment for patients with chronic glomerulonephritis is substantially different from that used for RA or asthma. Patients with chronic glomerulonephritis are initially treated with a large dose of prednisolone daily for approximately 10 weeks, followed thereafter by alternate-day administration. Such treatment has been shown to result in significant loss of BMD in the lumbar spine and marked reductions in biochemical markers of bone formation. However, bone resorption is not enhanced with prednisolone, which suggests that decreased BMD in

patients treated with prednisolone is a result of suppressed bone formation and not increased bone resorption. (Yonemura et al. 2000)

Renal failure patients are at risk for vitamin D deficiency owing to their inability to take vitamin D supplements. Pharmacologic doses of vitamin D may cause acute renal failure secondary to hypercalcemia associated with vitamin D intoxication. (Yonemura et al. 2000) One study has shown that the risk of hip fracture among white patients with end-stage renal disease is considerably higher than that in the general population, independent of age and gender. (Alem et al. 2000)

Pulmonary Disorders

Long-term glucocorticoid treatment, whether oral or inhaled, is widely prescribed for patients with chronic obstructive pulmonary disease (COPD), asthma, and allergic rhinitis. In the past two decades, prescriptions for inhaled glucocorticoids have increased by 139% to 326%, and the number of prescriptions is expected to steadily increase as guidelines advocating inhaled glucocorticoids as first-line therapy for persistent asthma (National Asthma Education Prevention Program 1997) are implemented into US and worldwide clinical practice. (Goldstein et al. 1999) In addition to the risks posed by chronic glucocorticoid treatment, patients with respiratory diseases may have an increased risk for osteoporosis due to the sedentary lifestyle imposed by their underlying pulmonary state.

Although chronic glucocorticoid therapy is effective in controlling the inflammatory processes in asthma, the development of osteoporosis secondary to chronic glucocorticoid use is of increasing concern, and the risk may be greater than commonly perceived. The prevalence of osteopenia/osteoporosis has been shown to be as high as 62% in asthmatic patients. (Goldstein et al. 1999) Data from a community database showed that in patients treated with oral glucocorticoids for ≥ 1 year, 86% demonstrated a decrease in BMD. These decreases were dose related and were observed in 80% of high-dose, 71% of medium-dose, and 33% of low-dose patients (Reddy et al. 1998). The incidence of glucocorticoid-induced bone loss in COPD patients is also quite high. It is likely that the incidence and prevalence of glucocorticoid-induced bone loss will increase as the use of chronic oral and high-dose inhaled glucocorticoid therapy rises in parallel with the aging of the at-risk population. (Goldstein et al. 1999)

Post-transplantation Patients

Glucocorticoid-induced osteoporosis is a common finding in adult organ transplant patients (Braith et al. 2000; Cayco et al. 2000; Spira et al. 2000). Cayco et al. (2000) found a 44% incidence of either osteoporosis or osteopenia in renal transplant patients, and Giannini et al.

(2000) reported a 46% incidence of osteoporosis in liver transplant patients a mean of 11 months after transplantation.

Glucocorticoids are an independent predictor of low bone mass, and their effects on bone in post-transplant patients, as in patients with other conditions, are exerted in a dose-dependent fashion. (Giannini et al. 2000) Major factors in the development of bone loss after transplantation, in addition to the use of high-dose glucocorticoids, include immobilization and use of cyclosporine, which has a deteriorative effect on bone. Low pre-transplant bone mass is also a major predictor of post-transplant fractures. (Wolfhagen et al. 2000) In addition, PTH levels are elevated in transplant recipients, and hyperparathyroidism is associated with decreased BMD. (Cayco et al. 2000; Kokado et al. 2000; Heaf et al. 2000) Poor nutritional status and hypogonadism may also affect bone metabolism, especially in the early post-transplantation phase (Giannini et al. 2000)

Dramatic reductions in BMD occur early in the postoperative period (<6 months), coincident with administration of bolus doses of glucocorticoids as part of the immunosuppression regimen; elevated rates of bone resorption contribute importantly to this process. (Cayco et al. 2000; Spira et al. 2000; Leidig-Bruckner et al. 2001) Decreases in spinal BMD of 4% to 24% have been seen during the first year after liver or lung transplantation (Wolfhagen et al. 2000; Spira et al. 2000). Several investigators have found that these decreases in BMD occur despite vitamin D and calcium supplementation. (Spira et al. 2000; Giannini et al. 2000; Leidig-Bruckner et al. 2001) Although bone mass increases after the first year post transplant (Wolfhagen et al. 2000), it does not return to pretransplant levels, and transplant patients remain indefinitely at an increased risk of osteoporotic injury (Braith et al. 2000; Giannini et al. 2000).

Lumbar vertebrae are particularly vulnerable to steroid-induced osteoporosis, with BMD deficits of 10% to 20% observed less than 60 days after transplantation. (Braith et al. 2000) This dramatically decreased BMD is associated with a high incidence of osteoporotic fractures post transplant. (Spira et al. 2000; Giannini et al. 2000; Leidig-Bruckner et al. 2001) Two studies showed a fracture rate of 11% to 35% in the first year (Wolfhagen et al. 2000; Leidig-Bruckner et al. 2001), and in two other studies with 7- and 3-year follow-up, osteoporotic fractures occurred in 35% and 65% of transplant patients, respectively; 50% to 77% of these patients experienced their first fracture within the first year after transplantation. (Eastell et al. 1991; Feller et al. 1999) Radiologic evidence of long-bone fractures has been reported in up to 44% of adult transplant recipients, and vertebral compression fractures have been reported in 18% to 50% of adult transplant patients receiving a combination of steroids and cyclosporine. (Braith et al. 2000; Shane et al. 1993; Spira et al. 2000)

Vertebral fractures frequently occur in the first 12 months after transplantation. (Giannini et al. 2000; Leidig-Bruckner et al. 2001) In one study most transplant patients who experienced a vertebral fracture had two or more fractures, with pronounced vertebral height reduction. (Leidig-Bruckner et al. 2001) Because patients with two or more vertebral fractures have a worse outcome than those with only one vertebral fracture, prevention of osteoporosis is of utmost importance in transplant patients. (Leidig-Bruckner et al. 2001)

An elevated rate of bone turnover is one cause of rapid bone loss after transplantation, and therefore anti-resorptive drugs may be one way to prevent or treat post-transplantation osteoporosis. (Leidig-Bruckner et al. 2001) Because it is difficult to identify patients at high risk for osteoporosis or fracture, it is recommended that all patients undergoing transplantation receive preventive osteoporosis treatment beginning either before or directly after surgery. (Leidig-Bruckner et al. 2001)

PREVENTION AND TREATMENT OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Osteoporosis is largely preventable owing to advances in our understanding of its causes, diagnosis, and treatment. (NIH Panel, 2001) However, despite the fact that many physicians are aware of the incidence of glucocorticoid-induced bone loss and some initiate therapy when osteoporosis is diagnosed, more than 50% of patients receiving chronic high-dose oral glucocorticoid therapy are not evaluated for osteoporosis (Bell et al. 1997), and as few as 14% of patients receiving high-dose chronic glucocorticoid treatment receive concomitant treatment for osteoporosis (Walsh et al. 1996). Many patients on long-term glucocorticoid therapy receive no prophylaxis against bone loss (Saag et al. 1999; Valentine and Sninsky 1999; Brand et al. 1999; Soucy et al. 2000; Walsh et al. 1996) Clearly, because of the significant and widespread consequences of osteoporosis, physicians must be proactive in helping patients maintain BMD and prevent additional bone loss. Contrary to previous recommendations, the identification and treatment of patients at risk for osteoporosis may be valuable even among very elderly people. (Gabriel 1996)

Patient Evaluation

A detailed patient history and physical examination assessing presence and history of fractures, kyphosis, back pain, height loss, motor coordination (to determine the risk of falls), and previous exposure to glucocorticoid therapy should be performed in each patient to determine that patient's major risk factors for osteoporosis (see Table 2). (Goldstein et al. 1999) BMD measurements should be obtained in all patients at baseline and regularly thereafter to assess risk for osteoporosis (NIH Panel 2001). The current gold standard for BMD measurement is dual-energy x-ray absorptiometry (DEXA) of the lumbar spine, femoral neck, and femoral trochanter (Blair et al. 2000); at follow-up visits the percentage change from baseline in BMD at these sites is determined. However, BMD does not directly correlate with decreased fracture risk, and other factors such as bone strength and rate of turnover may also contribute to fragility. (Blair et al. 2000) In addition, patients at risk for GIO may have a higher risk of fracture at a given bone density than patients at risk for osteoporosis from other causes. (Blair et al. 2000)

Prevention of Osteoporosis

Both glucocorticoid dose and duration require continual re-evaluation to minimize the patient's cumulative dose. If possible, clinicians should try to maximize the use of inhaled and topical corticosteroids before proceeding to the oral form. Obvious preventive measures include smoking cessation, maintenance of healthy body weight, regular weight-bearing exercise, decreased alcohol consumption, sodium restriction, and increased dietary calcium intake. Most patients

require additional calcium supplementation to meet the recommended 1500 mg/d, and those at risk may also require vitamin D₃ supplements; the optimal vitamin D dosage is not known but is thought to be 400 to 1000 IU/d (NIH Panel 2001; Blair et al. 2000). However, even with appropriate supplementation, 1 in 6 patients treated with glucocorticoids will experience a radiographically detectable vertebral fracture within 12 months, and therefore, alternative regimens are needed.

Estrogen, vitamin D and its analogues, and calcitonin have prevented bone loss in patients treated with glucocorticoids in some (Buckley et al. 1996; Hall et al. 1994; Hahn et al. 1979; Sambrook et al. 1993) but not all (Adachi et al. 1996; Dykman et al. 1984; Healey et al. 1996) trials. Currently the use of risedronate, the only bisphosphonate approved for the prevention of GIO, offers the most promise of any available preventive therapy. (Blair et al. 2000)

Treatment of Osteoporosis

Prevention and treatment are closely related, and an individualized approach is recommended (NIH Panel 2001; Baxter 2000). Patients should be encouraged to exercise, as physical activity is necessary for bone acquisition and maintenance, and trials of exercise in older adults have shown significant reductions in the risk of fracture (NIH Panel 2001). Calcium and vitamin D modulate age-related increases in PTH levels and bone resorption, and optimal treatment of osteoporosis with any drug therapy requires supplementation with calcium and vitamin D to recommended levels (NIH Panel 2001).

However, calcium supplementation alone does not prevent bone loss, and calcitonin is seldom potent enough to have a clinically significant impact. (Manolagas and Weinstein 1999) Along with preventive measures such as risk factor modification (eg, smoking cessation) and adequate calcium and vitamin D₃ intake, treatment may include hormone replacement, when appropriate, and bisphosphonates. Hormone-replacement therapy has shown efficacy with regard to increasing BMD, but there have been no trials of estrogen therapy with hip fracture as the primary outcome. (NIH Panel, 2001) Less-proven treatments such as thiazide diuretics, anabolic steroids, and fluoride may also be considered in some populations (Blair et al. 2000). Unfortunately, however, with the exception of bisphosphonates, none of these treatments have been satisfactory, and none has proven anti-fracture efficacy in patients with GIO. In fact, for most patients, the benefit provided by the modest gains in BMD produced by these treatments are outweighed by serious side effects.

Although the American College of Rheumatology (1996) recommends the use of bisphosphonates only in patients for whom hormone-replacement therapy is contraindicated, newer treatment guidelines published by the United Kingdom Consensus Group (Eastell et al.

1998) emphasize that of all treatment options, bisphosphonates have demonstrated the most compelling BMD data and should be considered first-line therapy. (Blair et al. 2000) A recent meta-analysis showed that bisphosphonates are significantly and substantially more efficacious than either calcitonin or vitamin D and calcium. (Amin et al. 1998)

Bisphosphonate Therapy

All of the bisphosphonates are effective in preventing bone loss and increasing bone mass in patients with osteoporosis. (Cunnane and lane 2000) Bisphosphonates inhibit bone resorption (Cunnane and Lane 2000) and therefore offer a treatment that directly counters the effects of glucocorticoid therapy. Because they reverse the increase in osteocyte and osteoblast apoptosis caused by glucocorticoids, bisphosphonates may have a more specific role in treatment of patients with GIO than in other patient populations. (Reid 2000)

Bisphosphonates increase BMD at the spine and hip in a dose-dependent manner and consistently reduce the risk of fractures by 30% to 50%. These results are seen even in patients who have already lost bone. A recent literature review showed that risedronate not only prevented vertebral bone loss in patients who had not received previous steroid treatment, but also caused gains in bone mass in patients treated with steroids for >3 months who had already lost bone. (Blair et al. 2000)

All bisphosphonates have a low oral bioavailability (typically <5% on an empty stomach) and must be taken in a fasting state with water, at least 30 minutes before food and separated by several hours from ingestion of mineral supplements or antacids. The patient should remain upright for at least 30 minutes after administration. (Reid 2000; Blair et al. 2000) Absorption is significantly reduced if the drug is taken with calcium, food, or beverages other than water. Bisphosphonates are not metabolized and are excreted unchanged in the urine. (Cunnane and Lane 2000). Caution should be used in renal failure patients.

Overall, adverse events are minimal and include nausea and upper gastrointestinal inflammation, particularly with alendronate; bronchoconstriction may occur in patients with asthma. (Cunnane and Lane 2000) For each of the three oral bisphosphonates, the relative risk of discontinuing medication due to an adverse event is not statistically significant. (NIH Panel 2001)

The individual members of the bisphosphonate group differ primarily in their route of administration, their side effects, and their anti-resorptive potency. (Reid 2000) The anti-resorptive properties increase approximately 10-fold between generations (Cunnane and Lane 2000), with preclinical studies showing that risedronate is 1000 times more effective than etidronate as an antiresorptive agent. (Eastell et al. 2000)

Etidronate. Etidronate, a first-generation bisphosphonate, is approved for treatment of Paget's disease but not osteoporosis. (Goldstein et al. 1999) Although it improves spinal BMD, it

interferes with bone mineralization when given at doses that would be used clinically for treatment of osteoporosis. (Crandall 2001) Thus it must be given intermittently to avoid drug-induced defects in mineralization. (Manolagas and Weinstein 1999) More recent agents do not manifest this characteristic. (Crandall 2001)

Alendronate. Alendronate, a second-generation bisphosphonate, is approved for treatment of Paget's disease, postmenopausal osteoporosis, and glucocorticoid-induced bone loss, but not for prevention of GIO. (Goldstein et al. 1999) Therapy with oral alendronate is more attractive than treatment with etidronate because of greater safety, but gains in BMD are still modest (Manolagas and Weinstein 1999)

The combined results of two pivotal double-blind, placebo-controlled, multicenter trials of alendronate in the prevention and treatment of GIO were reported by Saag et al. in 1998. A total of 477 patients aged 17 to 83 years who required long-term (≥ 1 year) glucocorticoid treatment with at least 7.5 mg of prednisone or its equivalent were randomly assigned to receive placebo or alendronate (5 or 10 mg) for 48 weeks. At the end of treatment, total-body BMD and BMD at the lumbar spine, femoral trochanter, and femoral neck were significantly increased in those who received a daily alendronate dose of 5 or 10 mg, compared with those who received placebo. Increases in BMD did not differ according to age or sex of the patient, underlying disease, dose or duration of glucocorticoid treatment, or lumbar spine BMD at baseline. Approximately 80% of patients who received alendronate experienced an increase in BMD, compared with 45% of those who received placebo, and bone turnover was reduced in the alendronate groups. However, this increased bone mass and reduced turnover did not translate into a reduced incidence of fractures. (Saag et al. 1998, 1999)

Alendronate may carry an increased risk of gastrointestinal adverse events (Blair et al. 2000; Peter et al. 1998). Graham and Malaty (1999) reported a 38% incidence of esophageal damage in healthy volunteers who took alendronate, compared with those who took placebo. There was a marked difference in severity of mucosal damage, in that antral ulcers and erosions occurred in patients receiving alendronate, but not in those receiving placebo. (Graham and Malaty 1999) These results were contradicted in a larger study by Bauer et al. (2000) However, a recent literature review suggests that the incidence of gastrointestinal adverse events with alendronate may be as high as 15% in clinical practice, despite low incidence rates in phase 3 trials, possibly because of administration errors. (Blair et al. 2000)

Risedronate. Risedronate, a third-generation bisphosphonate, is approved for treatment of Paget's disease and postmenopausal osteoporosis. In addition, it is the only bisphosphonate approved for both the prevention and treatment of GIO. (Crandall 2001; Reid 2000)

Risedronate is not associated with the diarrhea seen in patients receiving etidronate or with the esophageal erosions seen in patients receiving alendronate. (Reid 2000) One comparison

of esophageal and gastroduodenal effects of risedronate and alendronate treatment in postmenopausal women showed that at doses used for the treatment of osteoporosis, risedronate was associated with a significantly lower incidence of gastric ulcers than was alendronate. (Lanza et al. 2000)

Risedronate can be administered in lower dosages than other anti-resorptive bisphosphonates and is more effective than etidronate in relieving pain in patients with Paget's disease. (Goa and Balfour 1998) Furthermore, risedronate 2.5 mg/d has been shown to prevent bone loss in postmenopausal women treated with glucocorticoids for RA, and the incidence of gastrointestinal or other adverse events is similar in patients treated with risedronate or placebo. (Goa and Balfour 1998)

A review of 16 clinical trials showed that in patients with postmenopausal and glucocorticoid-induced osteoporosis, risedronate prevented postmenopausal bone loss, decreased fracture in those with established postmenopausal osteoporosis, effectively treated Paget's disease, and prevented glucocorticoid-induced bone loss. (Crandall 2001) In addition, a pooled data analysis demonstrated a greater than 50% reduction in fractures in the first year of treatment with risedronate. (Reid 2000)

Four studies have examined the efficacy of risedronate in the prevention and treatment of bone loss and osteoporosis in patients receiving long-term glucocorticoid treatment. (Cohen et al. 1999; Eastell et al. 2000; Wallach et al. 2000; Reid et al. 2000) Details of each study follow, but in general the patients studied were males and females aged 18 to 85 years, with a variety of diseases, although in one trial (Eastell et al. 2000), patients consisted of postmenopausal RA patients only. All studies examined the percentage change from baseline in BMD of the lumbar spine and proximal femur as measured by DEXA. Lateral thoracic and lumbar radiographs were performed to assess the incidence of fractures. All studies showed that risedronate significantly increased BMD (**Table 5**). In addition, three of the four studies showed that risedronate 5 mg/d significantly decreased vertebral fracture risk (Wallach et al. 2000; Reid et al. 2000) or showed a trend toward reduction in fracture risk (Cohen et al. 1999). Risedronate was well tolerated, with adverse events, including gastrointestinal adverse events, equivalent to those in the placebo group. This was true even though many patients were also receiving nonsteroidal anti-inflammatory drugs (NSAIDs) and patients with gastrointestinal tract disease were not excluded. The incidence of back pain and arthralgia was slightly greater in patients receiving risedronate 5 mg/d, but in general these effects were mild and did not lead to discontinuation of treatment.

Cohen et al. (1999) conducted a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 228 ambulatory men and women who were initiating long-term glucocorticoid treatment. Patients received either risedronate (2.5 or 5 mg/d) or placebo for

12 months, and all patients received 500 mg of elemental calcium supplementation daily. Mean daily dose of prednisone or its equivalent ranged from 20.4 to 21.7 mg.

Results showed that daily oral risedronate therapy prevented significant bone loss relative to placebo in patients initiating glucocorticoid treatment for a variety of disorders. Responses within subgroups were consistent with those in the overall population. Risedronate 5 mg produced significant treatment effects in BMD of the lumbar spine, femoral neck, and femoral trochanter in men and postmenopausal women. A therapeutic effect was also noted in premenopausal women who received risedronate 5 mg/d, but the changes were not significant. The effect on BMD in the 2.5-mg risedronate group was smaller than, but consistent with, that seen in the 5-mg risedronate group. A trend toward a reduction in the incidence of vertebral fractures was seen in both men and postmenopausal women; none of the premenopausal women sustained a fracture. In addition, the quality of bone formed during risedronate treatment was normal, with no evidence of impaired mineralization. Patients who received placebo lost, on average, 3% of bone mass at the lumbar spine and proximal femur. Comparisons between this study and others in which patients received higher doses of calcium (Saag et al. 1998; Sambrook et al. 1993) suggest that higher doses of calcium supplementation would not have provided greater protection from bone loss in patients receiving placebo.

A two-center, 2-year, double-blind, placebo-controlled study conducted by Eastell and co-workers (2000) assessed risedronate's effect on BMD in 120 postmenopausal women with RA who were receiving an average daily prednisone dose of at least 2.5 mg. Patients were assigned to treatment with placebo or risedronate (2.5 mg/d or cyclical 15 mg risedronate [15 mg daily for 2 weeks, followed by 10 weeks on placebo]). Patients received study drug for 96 weeks, then underwent a 48-week nontreatment follow-up, for a total of 144 weeks. Mean BMD at baseline was 2.5 SD below the mean normal value.

By the end of the study, significant bone loss was seen in placebo patients, whereas BMD was maintained in those who received risedronate 2.5 mg/d. The cyclical risedronate regimen was less efficacious than the daily 2.5-mg regimen in maintaining BMD at the lumbar spine but was equally efficacious in maintaining BMD at the femoral neck and trochanter; differences between the two risedronate treatments were not significant. Risedronate discontinuation resulted in bone loss at all sites, and this loss was significant in the lumbar spine. The incidence of vertebral fractures did not differ significantly among treatment groups.

Wallach et al. (2000) reported the results of two randomized, double-blind, placebo-controlled studies conducted in parallel under similar protocols and combined for analysis. Subjects were 509 ambulatory men and women receiving glucocorticoid treatment equivalent to 7.5 mg of prednisone or more. Patients were randomly assigned to receive placebo, risedronate 2.5 mg/d, or risedronate 5 mg/d for 12 months.

Results at 12 months showed that risedronate 5 mg significantly increased or maintained BMD relative to placebo at the lumbar spine, femoral neck and trochanter, and distal radius. The risedronate 2.5-mg dose was less efficacious than risedronate 5 mg; differences in BMD in patients receiving risedronate 2.5 mg and those receiving placebo were significant at the lumbar spine but not at other skeletal sites. Placebo patients had a 16% incidence of vertebral fractures in the first year; by comparison, the effect of risedronate 5 mg on lumbar spine BMD was associated with a 70% reduction in the risk of new vertebral fractures. Bone resorption was also greatly reduced in patients who received risedronate. Effects in men and postmenopausal women were similar, with smaller effects seen in premenopausal women, possibly because of the small number of such patients in this study or because of the effects of endogenous estrogen.

A multicenter, double-blind, placebo-controlled, parallel-group study was conducted by Reid and colleagues (2000) to evaluate the efficacy, safety, and tolerability of risedronate in 290 men and women who had been receiving high-dose oral glucocorticoid therapy for an average of 5 years. Patients were randomly assigned to receive placebo or risedronate (2.5 or 5 mg) daily for 12 months.

Results showed a significant (3%) gain in lumbar BMD with risedronate 5 mg compared with placebo; estimated gains in BMD at the femoral neck and trochanter were approximately 1% to 2%. The 2.5-mg risedronate dose was less effective but still better than placebo. Although increases in BMD were observed in all patient subgroups, gains in men and postmenopausal women were statistically significant; those in premenopausal women were not. Placebo patients did not demonstrate a significant decrease in BMD over the 12-month study, possibly because the greatest loss in BMD occurs in the first 6 months of treatment with glucocorticoids, and mean treatment time was 5 years. The estimated reduction in fracture risk in both risedronate groups, compared to placebo, was 70%.

The cumulative results of these four studies show that treatment with risedronate increased BMD in both men and women aged 18 or older who were receiving glucocorticoid treatment; treatment effects were seen across a wide range of conditions requiring such therapy. In addition, risedronate had a positive effect on fracture risk in patients with GIO. Risedronate was also well tolerated, with adverse events equivalent to those in patients who received placebo.

CONCLUSIONS AND RECOMMENDATIONS

Because subjects in clinical trials may not always be representative of community-based populations, an individualized approach to treatment is advised. (NIH Panel, 2001). Prescribers of oral, inhaled, and intranasal corticosteroids should be aware of the potential for long-term systemic effects and should make every effort to prescribe the lowest possible effective maintenance dosage. (Lipworth and Jackson 2000) In addition, all patients beginning long-term

(>6 months) treatment with glucocorticoids (ie, ≥ 5 mg/d prednisone) should undergo a baseline bone density measurement using DEXA to determine the risk of osteoporosis and to monitor the efficacy of the chosen preventative agent during the course of therapy. BMD measurements should be repeated every 6 to 12 months, depending on initial bone mass and patient risk factors. If at any point BMD has decreased by >5% from baseline, the initial choice of therapy should be changed or expanded. (Blair et al. 2000; Baxter 2000)

Because the majority of bone loss occurs during the first 6 months of treatment, clinicians must be vigilant in developing a prevention plan in advance of treatment, preferably before the glucocorticoid prescription is given to the patient. Such a plan should include exercise, gonadal therapy, vitamin D and calcium supplementation, measurement of 24-hour urinary Ca^{++} levels, and pharmacologic prophylaxis against osteoporosis. (Baxter 2000; Blair et al. 2000)

Bisphosphonates, particularly risedronate, offer the most promise as first-line therapy for patients receiving long-term glucocorticoid treatment. (Blair et al. 2000) Of the various agents investigated to date, the bisphosphonates have produced the most consistently positive results in glucocorticoid-treated subjects. (Reid 2000; Baxter 2000) In addition, these agents can be used in virtually all glucocorticoid-treated patients, including the young and sex hormone-replete. (Reid 2000) They have theoretical advantages over estrogen replacement therapy in that they are bone specific, have minimal adverse effects, and have no known carcinogenic potential. (Crandall 2001)

Risedronate treatment not only prevents the rapid bone loss associated with the first months of long-term glucocorticoid treatment, it significantly increases bone density in patients receiving such treatment. (Wallach et al. 2000) In addition, it is the only agent that has provided evidence of a reduced fracture rate (Reid 2000). In studies risedronate was effective regardless of the duration of previous corticosteroid therapy, underlying disease, or gender, which suggests that the findings are applicable to a wide spectrum of patients receiving glucocorticoid treatment. (Wallach et al. 2000)

Physicians can maximize bone density in patients receiving glucocorticoid treatment by starting them on risedronate, the only agent currently approved for the prevention of GIO, at the time patients begin steroid therapy. However, the safety and efficacy of bisphosphonates have not been evaluated in children and young adults, and caution is urged when prescribing these agents for patients <18 years old. (NIH Panel 2001)

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REFERENCES

- Abitbol V, Roux C, Chaussade S, et al. Metabolic bone assessment in patients with inflammatory bowel disease. *Gastroenterology*. 1995;108(2):417–422.
- Adachi JD, Bensen WG, Bianchi F, et al. Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: A 3-year followup. *J Rheumatol*. 1996;23:995–1000.
- Adinoff AD, Hollister JR. Steroid-induced fractures and bone loss in patients with asthma. *N Engl J Med*. 1997;337:382–387.
- Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, Wong C, Stehman-Breen C. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int*. 2000;58(1):396–399.
- American College of Rheumatology Task Force on Osteoporosis Guidelines. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheum*. 1996;39:1791–1801.
- Amin S, LaValley MP, Simms RW, Felson DT. A meta-analysis ranking efficacy of treatments for corticosteroid-induced osteoporosis (CSOP). *Arthritis Rheum*. 1998;41(Suppl):S137.
- Ardizzone S, Bollani S, Bettica P, Bevilacqua M, Molteni P, Bianchi Porro G. Altered bone metabolism in inflammatory bowel disease: There is a difference between Crohn's disease and ulcerative colitis. *J Intern Med*. 2000;247(1):63–70.
- Bauer DC, Black D, Ensrud K, et al. Upper gastrointestinal tract safety profile of alendronate: The Fracture Intervention Trial. *Arch Intern Med*. 2000;160(11):517–525.
- Baxter JD. Advances in glucocorticoid therapy. *Adv Intern Med*. 2000;45:317–349.
- Bell R, Carr A, Thompson P. Managing corticosteroid-induced osteoporosis in medical outpatients. *J R Coll Physicians Lond*. 1997;31:158–161.
- Bjarnason I, MacPherson A, MacKintosh C, Buxton-Thomas M, Forgacs I, Moniz C. Reduced bone density in patients with inflammatory bone disease. *Gut*. 1997;40(2):228–233.
- Blair MM, Carson DS, Barrington R. Bisphosphonates in the prevention and treatment of glucocorticoid-induced osteoporosis. *J Family Pract*. 2000;49(9):839–848.
- Bonala SB, Reddy BM, Silverman BA, Bassett CW, Rao YA, Amara S, Schneider AT. Bone mineral density in women with asthma on long-term inhaled corticosteroid therapy. *Ann Allergy Asthma Immunol*. 2000;85(6 pt 1):495–500.
- Boutsen Y, Jamart J, Esselinckx W, Stoffel M, Devogelaer J-P. Primary prevention of glucocorticoid-induced osteoporosis with intermittent intravenous pamidronate: A randomized trial. *Calcif Tissue Int*. 1997;61:266–271.
- Braith RW, Howard C, Fricker J, Mitchell M, Edwards DG. Glucocorticoid-induced osteopenia in adolescent heart transplant recipients. *J Heart Lung Transplantation*. 2000;19(9):840–845.
- Brand CA, Jolley D, Tellus M, Muirden KD, Wark JD. Risk factors for osteoporosis and fracture in patients attending rheumatology outpatient clinics. *Aust N Z J Med*. 1999;29(2):197–202.

- Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Calcium and vitamin D3 supplementation prevents bone loss in the spine secondary to low-dose corticosteroids in patients with rheumatoid arthritis: A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 1996;125:961–968.
- Cayco AV, Wysolmerski J, Simpson C, et al. Posttransplant bone disease: Evidence for a high bone resorption rate. *Transplantation.* 2000;70(12):1722–1728.
- Cohen S, Levy RM, Keller M, et al. Risedronate therapy prevents corticosteroid-induced bone loss—a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum.* 1999;42:2309–2318.
- Cowan FJ, Warner JT, Dunstan FDJ, Evans WD, Gregory JW, Jenkins HR. Inflammatory bowel disease and predisposition to osteopenia. *Arch Dis Child.* 1997;76:325–329.
- Crandall C. Risedronate: A clinical review. *Arch Intern Med.* 2001;161:353–360.
- Cunnane G, Lane NE. Steroid-induced osteoporosis in systemic lupus erythematosus. *Rheum Dis Clin North Am.* 2000;26(2):311–329.
- Dequeker J, Maenaut K, Verwilghen J, Westhovens R. Osteoporosis in rheumatoid arthritis. *Clin Exp Rheumatol.* 1995;13(Suppl 12):S21–S26.
- Diamond TH, Stiel DA, Lunzer M. Hepatic osteodystrophy. *Gastroenterology.* 1989;96:213–221.
- Dykman TR, Haralson KM, Gluck OS, et al. Effect of oral 1,25-dihydroxyvitamin D and calcium on glucocorticoid-induced osteopenia in patients with rheumatic diseases. *Arthritis Rheum.* 1984;27:1336–1343.
- Eastell R, Dickson ER, Hodgson SF, et al. Rates of vertebral bone loss before and after liver transplantation in women with primary biliary cirrhosis. *Hepatology.* 1991;14:296–300.
- Eastell R, Reid DM, Compston J, et al. A UK consensus group on management of glucocorticoid-induced osteoporosis: An update. *J Intern Med.* 1998;244:271–292.
- Eastell R, Devogelaer J-P, Peel NFA, et al. Prevention of bone loss with risedronate in glucocorticoid-treated rheumatoid arthritis patients. *Osteoporosis Int.* 2000;11:331–337.
- Esteban NV, Loughlin T, Yergey AL, et al. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. *J Clin Endocrinol Metab.* 1991;71:39–45.
- Fairney A. Bone loss and glucocorticoid therapy in patients with respiratory disease. *Thorax.* 1999;54(Suppl 2):S52–S57.
- Feller RB, McDonald JA, Sherbon KJ, McCaughan GW. Evidence of continuing bone recovery at a mean of 7 years after liver transplantation. *Liver Transplantation Surgery.* 1999;4:407–413.
- Fiter J, Nolla JM, Navarro MA, Gomez-Vaquero C, Rosei P, Mateo L, Roig-Escofet D. Weak androgen levels, glucocorticoid therapy, and bone mineral density in postmenopausal women with rheumatoid arthritis. *Joint Bone Spine.* 2000;67:199–203.
- Florkowski CM, Holmes SJ, Elliott JR, Donald RA, Espiner EA. Bone mineral density is reduced in female but not male subjects with Addison's disease. *N Z Med J.* 1994;107:52–53.

- Gabriel SE. Update on the epidemiology of the rheumatic diseases. *Curr Opin Rheumatol*. 1996;8(2):96–100.
- Giannini S, Nobile M, Ciuffreda M, et al. Long-term persistence of low bone density in orthotopic liver transplantation. *Osteoporos Int*. 2000;11:417–424.
- Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus. *Arthritis Rheum*. 1996;39:363–369.
- Goa KL, Balfour JA. Risedronate. *Drugs Aging*. 1998;13(1):83–91.
- Goldstein MF, Fallon JJ Jr, Harning R. Chronic glucocorticoid therapy–induced osteoporosis in patients with obstructive lung disease. *Chest*. 1999;116(6):1733–1749.
- Graham DY, Malaty HM. Alendronate gastric ulcers. *Aliment Pharmacol Ther*. 1999;13(4):515–519.
- Hahn TJ, Halstead LR, Teitelbaum SL, Hahn BH. Altered mineral metabolism in glucocorticoid-induced osteopenia: Effect of 25-hydroxyvitamin D administration. *J Clin Invest*. 1979;64:655–665.
- Hall GM, Daniels M, Doyle DV, Spector TD. Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. *Arthritis Rheum*. 1994;37:1499–1505.
- Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: Results from 394 patients in the Oslo County Rheumatoid Arthritis register. *Arthritis Rheum*. 2000;43(3):522–530.
- Heaf J, Tvedegaard E, Kanstrup IL, Fogh-Andersen N. Bone loss after renal transplantation: Role of hyperparathyroidism, acidosis, cyclosporine and systemic disease. *Clin Transplant*. 2000;14(5):457–463.
- Healey JH, Paget SA, Williams-Russo P, et al. A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arteritis and polymyalgia rheumatica. *Calcif Tissue Int*. 1996;58:73–80.
- Jardinet D, Lefebvre C, Depresseux G, Lambert M, Devogelaer J-P, Houssiau FA. Longitudinal analysis of bone mineral density in pre-menopausal female systemic lupus erythematosus patients: Deleterious role of glucocorticoid therapy at the lumbar spine. *Rheumatology*. 2000;39:389–392.
- Jeffcoate W. Assessment of corticosteroid replacement therapy in adults with adrenal insufficiency. *Ann Clin Biochem*. 1999;36:151–157.
- Kelts DG, Grand RJ, Shen G, et al. Nutritional basis of growth failure in children and adolescents with Crohn's disease. *Gastroenterology*. 1979;76:720–727.
- Kipen Y, Strauss BJG, Morand EF. Body composition in systemic lupus erythematosus. *Br J Rheumatol*. 1998;37:514–519.

Kipen Y, Briganti E, Strauss B, Will R, Morand EF. Three year follow-up of bone mineral density changes in pre-menopausal women with systemic lupus erythematosus. *J Rheumatol*. 1999;26:310–317.

Kokado Y, Takahara S, Ichimaru N, et al. Factors influencing vertebral bone density after renal transplantation. *Transpl Int*. 2000;13(Suppl 1):S431–S435.

Laan RF, van Riel PL, van de Putte LB, van Erning LJ, van't Hof MA, Lemmens JA. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. *Ann Intern Med*. 1993;119(10):963–968.

Laan RF, Jansen TL, van Riel PL. Glucocorticoids in the management of rheumatoid arthritis. *Rheumatology (Oxford)*. 1999;38–6–12.

Lanza FL, Hunt RH, Thomson AB, Provenza JM, Blank MA. Endoscopic comparison of esophageal and gastroduodenal effects of risedronate and alendronate in postmenopausal women. *Gastroenterology*. 2000;119(3):631–638.

Leidig-Bruckner G, Hosch S, Dodidou P, et al. Frequency and predictors of osteoporotic fractures after cardiac or liver transplantation: A follow-up study. *Lancet*. 2001;357:342–347.

Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy—a systematic review and meta-analysis [review]. *Arch Intern Med*. 1999;159:941–955.

Lipworth BJ, Jackson CM. Safety of inhaled and intranasal corticosteroids: Lessons for the new millennium. *Drug Safety*. 2000;23(1):11–33.

LoCasco V, Bonucci E, Imbimbo B, et al. Bone loss in response to long-term glucocorticoid therapy. *Bone Miner*. 1990;8:39–51.

Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: Pathogenesis and management. *Ann Intern Med*. 1990;112:352–364.

Manolagas SC, Weinstein RS. New developments in the pathogenesis and treatment of steroid-induced osteoporosis. *J Bone Miner Res*. 1999;14(7):1061–1066.

Michel BA, Bloch DA, Fries JF. Predictors of fractures in early rheumatoid arthritis. *J Rheumatol*. 1991;18:804–808.

Michel BA, Block DA, Wolfe F, Fries F. Fractures in rheumatoid arthritis: An evaluation of associated risk factors. *J Rheumatol*. 1993;20(10):1666–1669.

Morand EF. Corticosteroids in the treatment of rheumatologic diseases. *Curr Opin Rheumatol*. 2000;12:171–177.

National Asthma Education Prevention Program. Expert panel report 2: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Institutes of Health; 1997. Publication no. 97-4051.

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285(6):785–795.

- Nordin BEC, Robertson A, Seemark RF, et al. The relationship between calcium absorption, serum dehydroepiandrosterone and vertebral bone mineral density in postmenopausal women. *J Clin Endocrinol Metab.* 1985;60:651–657.
- Peacey SR, Guo C-Y, Robinson AM, et al. Glucocorticoid replacement therapy: Are patients over treated and does it matter? *Clin Endocrinol.* 1997;46:255–261.
- Peter CP, Handt LK, Smith SM. Esophageal irritation due to alendronate sodium tablets: Possible mechanisms. *Dig Dis Sci.* 1998;43(9):1998–2002.
- Petri M. Musculoskeletal complications of systemic lupus erythematosus in the Hopkins Lupus Cohort: An update. *Arthritis Care Res.* 1995;8(3):137–145.
- Pigot F, Roux C, Chaussade S, et al. Low bone mineral density in patients with inflammatory bowel disease. *Dig Dis Sci.* 1992;37(9):1396–1403.
- Reddy BM, Villar ME, Silverman BA, et al. Osteoporosis among adult asthma patients receiving chronic corticosteroid therapy [abstract]. *J Allergy Clin Immunol.* 1998;101:290.
- Reid DM, Hughes RA, Laan RFJM, et al. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: A randomized trial. *J Bone Miner Res.* 2000;15(6):1006–1013.
- Reid IR. Glucocorticoid-induced osteoporosis—mechanisms and management. *Eur J Endocrinol.* 1997;137:209–217.
- Reid IR. Glucocorticoid-induced osteoporosis. *Baillieres Clin Endocrinol Metab.* 2000;14(2):279–298.
- Rizzato G, Montemurro L. Reversibility of exogenous corticosteroid-induced bone loss. *Eur Respir J.* 1993;6(1):116–119.
- Robinson RJ, al-Azzawi F, Iqbal SJ, Kryswcki T, Almond L, Abrams K, Mayberry JF. Osteoporosis and determinants of bone density in patients with Crohn's disease. *Dig Dis Sci.* 1998;43(11):2500–2506.
- Saag KG, Emkey R, Schnitzer TJ, et al., for the Glucocorticoid-Induced Osteoporosis Intervention Study Group. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. *N Engl J Med.* 1998;339:292–299.
- Saag KG, Emkey R, Schnitzer TJ, et al., for the Glucocorticoid-Induced Osteoporosis Intervention Study Group. Alendronate increased bone mineral density but did not reduce new fractures in glucocorticoid induced osteoporosis. Clinical Alert. *Chest.* 1999;44:780–781.
- Sambrook PN, Eisman JA, Champion GD, et al. Determinants of axial bone loss in rheumatoid arthritis. *Arthritis Rheum.* 1987;30:721–728.
- Sambrook P, Birmingham J, Kelly P, et al. Prevention of corticosteroid osteoporosis—a comparison of calcium, calcitriol, and calcitonin. *N Engl J Med.* 1993;328:1747–1752.
- Scharla SH, Minne HW, Lempert UG, Leidig G, Hauber M, Raedsch R, Ziegler R. Bone mineral density and calcium regulating hormones in patients with inflammatory bowel disease (Crohn's disease and ulcerative colitis). *Exp Clin Endocrinol.* 1994;102(1):44–49.

- Shane E, Rivas C, Silverburg SJ, Kim TS, Staron RB, Bilezikian JP. Osteoporosis after cardiac transplantation. *Am J Med.* 1993;94:257–264.
- Silvennoinen J. Relationships between vitamin D, parathyroid hormone and bone mineral density in inflammatory bowel disease. *J Intern Med.* 1996;239(2):131–137.
- Singh RF, Muskelly CC. Inhaled corticosteroid-induced bone loss and preventive strategies. *J Am Osteopath Assoc.* 2000;100(7 Suppl):S14–S17.
- Sinigaglia L, Varenna M, Binelli L, Zucchi F, Ghiringhelli D, Gallazzi M, Limonta M, Zeni S, Fantini F. Determinants of bone mass in systemic lupus erythematosus: A cross-sectional study on premenopausal women. *J Rheumatol.* 1999;26(6):1280–1284.
- Smith BJ, Phillips PJ, Heller RF. Asthma and chronic obstructive airway diseases are associated with osteoporosis and fractures: A literature review. *Respirology.* 1999;4(2):101–109.
- Sorkness CA. Establishing a therapeutic index for the inhaled corticosteroids. Part II. Comparisons of systemic activity and safety among different inhaled corticosteroids. *J Allergy Clin Immunol.* 1998;102:S52–S64.
- Soucy E, Ballamy N, Adachi JD, Pope JE, Flynn J, Sutton E, Campbell J. A Canadian survey on the management of corticosteroid induced osteoporosis by rheumatologists. *J Rheumatol.* 2000;27(6):1506–1512.
- Spira A, Gutierrez C, Chaparro C, Hutcheon MA, Chan CK. Osteoporosis and lung transplantation: A prospective study. *Chest.* 2000;117(2):476–481.
- Tanaka Y, Watanabe K, Suzuki M, et al. Spontaneous production of bone-resorbing lymphokines by B-cells in patients with systemic lupus erythematosus. *J Clin Immunol.* 1989;9:415–420.
- Tattersfield AE, Town GI, Johnell O, Picado C, Aubier M, Braillon P, Karlstrom R. Bone mineral density in subjects with mild asthma randomised to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years. *Thorax.* 2001;56(4):272–278.
- Valentine JF, Sninsky CA. Prevention and treatment of osteoporosis in patients with inflammatory bowel disease. *Am J Gastroenterol.* 1999;94(4):878–883.
- van Staa TP, Leufkens HGM, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: Relationship to daily and cumulative doses. *Rheumatology.* 2000;39:1383–1389.
- van Vollenhoven RF, Engleman EG, McGuire JL. An open study of dehydroepiandrosterone in systemic lupus erythematosus. *Arthritis Rheum.* 1994;37:1305–1310.
- Wallach S, Cohen S, Reid DM, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. *Calcif Tissue Int.* 2000;67:277–285.
- Walsh LJ, Wong CA, Pringle M, et al. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: A cross sectional study. *Br Med J.* 1996;313:344–346.
- Wolfhagen FHJ, van Buuren HR, Vleggaar FP, Schalm SW. Management of osteoporosis in primary biliary cirrhosis. *Baillieres Clin Gastroenterol.* 2000;14(4):629–641.

Wong CA, Walsh LJ, Smith CJ, Wisniewski AF, Lewis SA, Hubbard R, Cawte S, Green DJ, Pringle M, Tattersfield AE. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet*. 2000;355(9213):1399–1403.

Yonemura K, Kimura M, Miyaji T, Hishida A. Short-term effect of vitamin K administration on prednisolone-induced loss of bone mineral density in patients with chronic glomerulonephritis. *Calcif Tissue Int*. 2000;66:123–128.

Zelissen PMJ, Croughs RJM, van Rijk PP, Raymakers JA. Effect of glucocorticoid replacement therapy on bone mineral density in patients with Addison's disease. *Ann Intern Med*. 1994;120:207–210.

TABLES

Table 1. Threshold Dosages for Inhaled Glucocorticoids Above Which Significant Bone Loss Occurs*

Glucocorticoid	Threshold Dosage
Bedesonide	800 µg/d
Fluticasone	750 µg/d
Flunisolide	1000 µg/d
Beclomethasone	1000 µg/d

*Data from Goldstein et al. (1999)

Table 2. Non–Disease-Specific Risk Factors for Osteoporosis

Previous fractures
Kyphosis
Back pain
Loss of height
Previous exposure to glucocorticoid treatment, and cumulative dose of such exposure
Postmenopausal status
Elderly age
Female sex
Asian ancestry
Previous bilateral oophorectomy
Slight body build
Tobacco and/or alcohol use
Decreased dietary vitamin D or calcium intake
Irregular menstrual history (<4 cycles/year or extreme physical activity resulting in hypoestrogenemia)
History of infertility or impotence (men)
Family history of osteoporosis
Exposure to anticonvulsants agents, thyroxin, lithium, heparin, methotrexate, warfarin, or cyclosporine

Table 3. Glucocorticoid-Induced Metabolic Effects Leading to Bone Loss

Direct effects on bone	Inhibition of osteoclast proliferation Inhibition of osteoclast attachment to bone matrix Suppression of osteoblast numbers, life span, and function (Cunnane and Lane 2000) Resultant inhibition of type I collagen and other proteins produced by osteoblasts
Effects on calcium metabolism	Decreased intestinal absorption of calcium and phosphate Increased urinary calcium excretion Resultant development of secondary hyperparathyroidism leading to increased bone resorption
Effects on sex hormones	Suppression of adrenal androgen and gonadal hormone release, leading to loss of anabolic effects of these hormones on bone formation and resorption
Other effects	Decreased muscle mass and strength, slowing or preventing exercise-induced benefits on bone formation, as well as reducing normal physical forces of muscle tension on bone Inhibition of release of growth factors such as insulin-like growth factor-1 (IGF-1) and transforming growth factor- β (TGF- β) exacerbate direct bone effects (Baxter 2000)

Modified from Goldstein et al. (1999).

IGF-1 = insulin-like growth factor-1; TGF- β = transforming growth factor- β .

Table 4. Summary of Additional Risk Factors for Osteoporosis in Conditions Treated with Glucocorticoids

Disease	Additional Risk Factors for Osteoporosis
Liver disorders (eg, PBC, PSC, chronic autoimmune hepatitis)	Hypogonadism, female sex, poor diet/malnutrition, low BMI (primary biliary cirrhosis)
Gastrointestinal disorders (eg, inflammatory bowel disease)	Malnutrition and related poor calcium intake/absorption,* low BMI, jejunal involvement, previous bowel resection, male sex (Crohn's disease)
Adrenal insufficiency (Cushing's disease, Addison's disease)	Sex hormone deficiency (Addison's disease), panhypopituitarism (Cushing's disease)
Rheumatoid arthritis	Deficiency in DHEAS and AND, physical inactivity, female sex, low BMI
Systemic lupus erythematosus	Vitamin D deficiency, physical inactivity, deficiency in DHEAS and AND, renal disease, menstrual irregularities, high-dose methotrexate therapy, acidosis, growth factor deficiencies
Renal diseases (eg, glomerulonephritis)	Vitamin D deficiency, white race (end-stage renal disease)
Pulmonary disorders (COPD, asthma, sarcoidosis)	Sedentary lifestyle, female sex
Transplant recipients	Post-transplant immobilization, high PTH levels, use of cyclosporine, vitamin D deficiency (renal transplant pts), poor nutritional status, hypogonadism, pre-transplant PBC and PSC, pre-transplant ischemic heart disease, pre-transplant vertebral fracture (liver transplant pts)

AND = androstenedione; BMI = body mass index; COPD – chronic obstructive pulmonary disease; DHEAS = dehydroepiandrosterone; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis.

*Study results are conflicting, though this appears to be a problem primarily in patients with small-bowel involvement or previous bowel resection.

Table 5. Percentage Change in BMD from Baseline in Studies of Risedronate in Glucocorticoid-Treated Patients

Study (No. of patients‡)	Treatment			
	Placebo	Risedronate 2.5 mg/d	Risedronate 5 mg/d	Cyclical Risedronate †
Cohen et al. (77/46/105)				
LS	-2.8 ± 0.5	-0.1 ± 0.7	0.6 ± 0.5	—
FN	-3.1 ± 0.7	-0.4 ± 0.7	0.8 ± 0.7	—
FT	-3.1 ± 0.7	-0.2 ± 0.7	1.4 ± 0.5	—
Eastell et al. (0/0/120)				
LS	-2.3 ± 0.9	1.0 ± 2.0	—	-2.8 ± 1.2
FN	-3.8 ± 1.0	-1.8 ± 0.9	—	-2.3 ± 1.3
FT	-4.6 ± 1.6	-1.2 ± 1.4	—	1.0 ± 2.3
Wallach et al. (184/70/255)				
LS	-1.0 ± 0.35	1.3 ± 0.41	1.9 ± 0.38	—
FN	-1.5 ± 0.41	-0.3 ± 0.39	1.3 ± 0.40	—
FT	-0.8 ± 0.51	-0.01 ± 0.39	2.0 ± 0.37	—
Reid et al. (109/25/156)				
LS	0.4 ± 0.4	1.9 ± 0.5	2.9 ± 0.5	—
FN	-0.3 ± 0.5	-0.2 ± 0.5	1.8 ± 0.5	—
FT	1.0 ± 0.6	0.1 ± 0.5	2.4 ± 0.5	—

*Values are mean ± SEM.

†15 mg daily for 2 weeks, followed by 10 weeks on placebo.

‡Men/premenopausal women/postmenopausal women who were enrolled in the study.

LS = lumbar spine; FN = femoral neck; FT = femoral trochanter.