PRACTICAL DRUG SAFETY

Drug Safety 2001; 24 (8): 607-624
0114-5916/01/0008-0607/$22.00/0

Corticosteroid-Induced Osteoporosis
Detection and Management

Jonathan D. Adachi and *Alexandra Papaioannou*

Department of Medicine, St Joseph's Hospital, McMaster University, Hamilton, Ontario, Canada

Contents

Abstract

Corticosteroid-induced osteoporosis is a major cause of morbidity and is the leading secondary cause of osteoporosis today. Unfortunately, despite this knowledge, patients receiving corticosteroid therapy are often not offered any preventative treatment. Recent research has focused attention on the critical role the osteoblast has played in the pathophysiology of corticosteroid-induced osteoporosis. In addition to an initial increase in bone resorption, there is evidence that corticosteroids induce osteoblast and osteocyte apoptosis and as a result are important contributors to bone loss. Interesting work has suggested that the bisphosphonates and calcitonin may help to prevent osteoblast apoptosis from occurring. Large scale randomised controlled trials have also been completed with a variety of therapeutic agents. Of the many different therapies, it is now clear that the bisphosphonates have the greatest evidence to support their use. Increases in bone mineral density when compared with a control group, not only at the spine but also at the hip, have been demonstrated. These studies have shown clinically significant reductions in vertebral fracture rates seen for the most part in postmenopausal

women. Other therapies may well be effective, as evidenced by maintenance of bone mass in the spine; however, maintenance of bone mass in the hip and reductions in fracture rate have yet to be demonstrated for many of these therapies. Given our current knowledge and the evidence that is outlined in this review, it is hoped that patients who require therapy with corticosteroids for more than 3 months will be offered appropriate preventative treatment.

It is estimated that between 30 and 50% of patients receiving long term corticosteroid therapy will experience fractures.[1,2] In fact, the risk of fracture increases by 50 to 100% in recipients of oral corticosteroids.[3,4] In particular, fractures at sites such as the spine and hip are associated with corticosteroid use.[5-7] Hip fractures are considered the most severe of all fractures, given that 20% of all hip fracture patients die within 6 months of the fracture.[8]

Corticosteroid-induced bone loss was discovered over 50 years ago,[9] but did not become a serious concern until corticosteroids began to be used therapeutically for common ailments such as allergies and inflammation. Today, corticosteroid use is the third leading cause of osteoporosis following loss of sex steroids and old age.[10]

Despite these facts, many patients receive inadequate treatment to prevent corticosteroid-induced osteoporosis, even though there are many available treatment options. One analysis found that 42% of postmenopausal women received no treatment to prevent osteoporosis while taking corticosteroids.[11] In another study, it was found that only 14% of patients receiving glucocorticoids were given therapy to prevent bone loss and fractures.[12] Osteoporosis prevention needs to become the standard of care for patients receiving long term corticosteroid treatment.

Many review papers have been written about corticosteroid-induced osteoporosis.[1,13-34] However, wide variation still exists in the treatment of osteoporosis.[35] This review paper outlines the latest recommended detection and management for corticosteroid-induced osteoporosis.

1. The Clinical Picture

Compared with postmenopausal osteoporosis, little is known about the pathophysiology of corticosteroid-induced osteoporosis. Most clinical trials that have examined corticosteroid-induced osteoporosis have involved patients with complicated systemic disorders of varying severity such as dysregulated immune and/or haematopoietic cell function. Often, as with rheumatoid arthritis, it is not possible to separate the effects of the primary disease from the corticosteroids with respect to bone loss.[36,37] Despite these difficulties, it is generally accepted that corticosteroids decrease bone formation and increase bone resorption. A reduction in bone formation may result from a decrease in osteoblast life span and cell apoptosis, while increased bone resorption may occur as a result of secondary hyperparathyroidism and reductions in gonadal hormones.

Corticosteroid-induced bone loss occurs rapidly within the first 6 to 12 months of beginning corticosteroid therapy; thereafter, the rate of loss slows to 2 to 3 times that of normal.[32,33,38] Bone loss may occur at rates as high as 5% during the first few months of glucocorticoid treatment, followed by about 2 to 3% annually.[10]

When corticosteroid-induced bone loss occurs, trabecular rather than cortical bone is affected more severely by corticosteroids.[7,39] As a consequence, fractures affecting the ribs, vertebrae and pelvis are particularly prevalent.[40] In 1 study, patients who were not taking corticosteroid therapy had a parallel reduction in bone mass at metaphyseal (trabecular bone) and diaphyseal (cortical bone) sites.[39] In contrast, patients who were taking more than 10 mg/day of prednisone had a greater degree of bone loss at the metaphyseal site, as compared with the diaphyseal site. Other investigators have confirmed these findings.[7]

There appears to be a close relationship between

the rate of bone loss and the dose of the drug. The risk of corticosteroid-induced osteoporosis increases as the cumulative corticosteroid dose increases,[41-43] but the shape of the dose-risk curve is unknown.[33] There is a dose-dependent response to the harmful effects of corticosteroids, and fracture risk increases rapidly upon initiation of corticosteroids and drops off quickly upon discontinuation.[44] Significant trabecular bone loss occurs with prednisone dosages greater than 7.5 mg/day in most patients.[33] However, in 1 study, bone loss rates increased with dosages of prednisone between 5 and 10 mg/day and with inhaled corticosteroids.[32] Thus, while lower doses of corticosteroids may be safer than higher doses, there is still no truly safe dose.

The risk of developing osteoporosis appears to be variable and depends on a number of factors including the dose of corticosteroid and the duration of exposure, gender of the patient and the menopausal status.[2] Corticosteroids alter the usual risk factors for osteoporosis. For instance, young people taking corticosteroids lose bone more rapidly than older people and premenopausal women in their 40s.[2] After menopause, fracture risk is greater for women taking corticosteroids, presumably because they are also susceptible to age and menopause-related bone loss.[33] Indeed, those individuals who are more than 70 years of age have a higher prevalence of fracture.[45] Men are equally susceptible to bone loss caused by corticosteroids.[2] In rheumatoid arthritis, it is likely that the inflammatory process and immobilisation contribute to bone loss.[42] Myopathy secondary to corticosteroid use and the underlying disease as well as concomitant drug therapy may contribute to the development of osteoporosis. Nonetheless, high doses of corticosteroids may well exacerbate this bone loss.[43]

However, not all of those who receive treatment with corticosteroids develop osteoporosis. This may be related to their underlying genetic susceptibility to fracture in the presence of corticosteroid use.[22]

2. Pathophysiology

Normally, old bone is continuously replaced by new bone. In fact, the entire adult skeleton is remodelled approximately every 10 years. Together, osteoblasts and osteoclasts form the basic multicellular unit, which is responsible for bone remodelling. Both osteoblasts and osteoclasts are derived from precursors originating in the bone marrow. Osteocytes, which are differentiated osteoblasts, are regularly spaced throughout the mineralised matrix and are thought to detect bone microdamage and transmit signals leading to its repair. Osteoclasts attach to bone and subsequently remove it by acidification and proteolytic digestion. Then, the osteoblasts move in and refill the resorption cavities through the process of new bone formation by secreting osteoid, which is eventually mineralised.

The cause of corticosteroid-induced osteoporosis is multifactorial and occurs in addition to normal age- and menopause-associated bone loss. There are 2 purported abnormalities in bone metabolism that develop in patients with corticosteroid-induced osteoporosis: the first is a reduction in bone formation and the second is an increase in bone resorption. A decrease in bone formation and an increase in bone resorption both lead to a decrease in bone mass, or osteoporosis. Reduced bone formation is attributed to the direct inhibition of osteoblastic function[46,47] and more recently to cell apoptosis.[10] Increased bone resorption is thought to be the result of the parathyroid hormone-mediated activation of osteoclasts.[48] This combination of increased resorption and decreased formation may well lead to trabecular perforation with a reduction in mechanical stability and increased risk of fracturing.[49]

2.1 Decrease in Bone Formation

Reduced bone formation has been attributed to the direct inhibitory effects of corticosteroids on osteoblast function. Moderate doses of corticosteroids inhibit both the synthesis of bone collagen by pre-existing osteoblasts and the conversion of pre-

cursor cells into functioning osteoblasts.[46,47,50,51] Furthermore, corticosteroids substantially reduce protein synthesis.[52] Histomorphometrically, this appears as a marked decrease in osteoid seams, a low mineral apposition rate measured by tetracycline labelling, and reduced mean wall thickness. The reduction in mean wall thickness is thought to be due to a shortened osteoblast life span.[47] A decrease in bone formation as evidenced by changes in bone turnover markers, particularly osteocalcin, has also been observed with the use of corticosteroids. However, osteocalcin decrease may overestimate the effects of corticosteroids on collagen synthesis.[53-58] Moreover, corticosteroids may affect osteoblasts by modulating their responses to parathyroid hormone, prostaglandins, cytokines, growth factors and 1,25-dihydroxyvitamin D3. In addition, the synthesis and activity of many local factors can be altered.[12] In comparison with normal aging, bone loss in corticosteroid-induced osteoporosis is greater because of an increased activation frequency (increased resorption and formation surfaces) and a more pronounced imbalance of remodelling.[47,59]

New findings by Manolagas and Weinstein[10] show that corticosteroid-induced osteoporosis may be due in part to increased apoptosis of osteocytes and osteoblasts. Corticosteroids have resulted in a 3-fold increase in osteoblast apoptosis in mouse vertebrae and induced apoptosis in 28% of the osteocytes in metaphyseal cortical bone. The fundamental problem in corticosteroid-induced osteoporosis appears to be a change in the number of bone-forming and regulating cells.

2.2 Increase in Bone Resorption

As compared with bone formation, the effects of corticosteroids on bone resorption have not been extensively studied and the results have been contradictory. It has been postulated that the influence of these agents on bone resorption is parathyroid hormone mediated.[48,60-63] For example, investigators have shown that after parathyroidectomy, the osteoclastic response to corticosteroids in animals is completely abolished, suggesting that increased bone resorption is, in large part, controlled by parathyroid hormone.[48] Others have suggested that an increase in bone resorption may result from secondary hyperparathyroidism and that this occurs as a consequence of decreased intestinal calcium absorption[64-68] and increased urinary excretion of calcium leading to relative hypocalcaemia.[69-71] However, the majority of studies have not found any increases in parathyroid hormone levels in patients receiving corticosteroid therapy. Furthermore, the role of parathyroid hormone has also been challenged on the basis of the assay needed to measure its serum level.[12] It has been argued that elevated parathyroid hormone levels were seen in assays that measured hormone fragments,[60-62,69] whereas no change was seen with assays that measured intact parathyroid hormone[56] or mid-region fragments.[42,55,72,73]

Altered calcium metabolism may lead to an increase in parathyroid secretion and to an increase in bone resorption. However, the effect of corticosteroids on net intestinal calcium absorption is also controversial. Results from radioisotope studies have indicated that calcium absorption may decrease,[74,75] increase[76] or remain unchanged[77] in response to corticosteroids. These contradictory results may be explained by the fact that corticosteroids act differently upon individual intestinal segments. For instance, it has been reported that while duodenal absorption is depressed,[67,68,78-80] these agents may stimulate colon absorption.[81,82] Furthermore, corticosteroids may alter calcium absorption in a dose-dependent manner.[83] These conflicting findings may also be the result of differences in corticosteroid dosages. In addition to decreased calcium absorption, corticosteroids may increase urinary excretion of calcium. In patients receiving long term corticosteroids, hypercalciuria is most probably due to increased skeletal calcium mobilisation and decreased renal tubular reabsorption, and results from a mechanism independent of parathyroid hormone.[55]

Corticosteroids may alter vitamin D metabolism, although the evidence in support of this is not convincing. Normal 25-hydroxyvitamin D3 levels

have been found in patients receiving corticosteroid therapy as compared with matched controls. Prednisone has been shown to depress calcium absorption from the gastrointestinal tract in normal individuals without depressing serum 25-hydroxyvitamin D3 levels.[63,84] Corticosteroids may act by reducing the serum levels of 1,25-dihydroxyvitamin D3;[85] nonetheless, they do not alter the conversion of 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3.[67,68] Seeman et al.[64] confirmed the absence of significant abnormalities in vitamin D metabolism. Godschalk et al.[86] found that corticosteroids reduced the number of vitamin D receptors, suggesting that this might be the mechanism by which these drugs antagonise the activity of vitamin D.

Corticosteroids alter gonadal function by inhibiting pituitary gonadotropin secretion. This, combined with their direct effect on the ovaries and testes, may lead to a reduction in the production of estrogen and testosterone. Corticosteroids blunt the secretion of luteinising hormone in response to luteinising hormone releasing hormone in both men and women.[87,88] They inhibit follicle-stimulating hormone-induced estrogen production in women and decrease testosterone production in men.[89-92] Circulating levels of androstenedione and estrone are further suppressed as a consequence of the reduced adrenal production of androstenedione, caused by the suppression of corticotropin and the resultant adrenal atrophy.[93] In fact, estrogen deficiency and corticosteroids may have an additive effect in increasing the rate of bone loss.[94]

3. Detection of Corticosteroid-Induced Osteoporosis

All patients taking corticosteroids should be assessed for their risk of developing osteoporosis.

3.1 Clinical Risk Assessment

The following risk factors should be examined in patients receiving corticosteroids: family history, hormonal status, fracture history, age, other medications that may interfere with normal bone metabolism, and lifestyle habits.[87,95-104] A family history should be completed to determine the existence of bone pathology in the patient's biological ancestry and should include history of osteoporosis, early menopause, longevity and fractures. All medications that interfere with normal bone metabolism should be noted (e.g. cyclosporin, phenytoin, etc.) and where possible replaced with other drugs that have less detrimental bone effects. Lifestyle risk factors, such as diet, alcohol use, physical activity and smoking, should be identified and treated appropriately.

3.2 Biochemical Assessment

A number of clinical biochemistry parameters are altered in patients with corticosteroid-induced osteoporosis. Bone-specific alkaline phosphatase and osteocalcin levels are low in most patients on corticosteroids. Doses of prednisone as low as 2.5mg suppress osteocalcin levels.[105] Measurements of urinary calcium levels are useful in assessing calcium balance, susceptibility to secondary hyperparathyroidism and potential treatment options for corticosteroid-treated patients.[54,55,69] With corticosteroid use, urine calcium excretion is initially high, then falls over time. Urinary hydroxyproline, pyridinoline, deoxypyridinoline and carboxy- and amino- telopeptide excretions are good indicators of bone resorption and, along with urinary calcium, may help predict those who will develop corticosteroid-induced osteoporosis.[106,107] There are laboratory studies that may be used to identify patients for specific interventions. If there is evidence of clinical hypogonadism, men should have their serum testosterone, follicle-stimulating hormone and luteinising hormone levels measured, and in oligo- or amenorrhoeic premenopausal women, levels of serum estradiol, follicle-stimulating hormone and luteinising hormone should be determined. Unfortunately, the usefulness of biochemical markers is limited, because none can reliably predict those who will lose bone mass and the degree to which it might be lost as a result of corticosteroid treatment. It may well be that a combination of baseline fracture prevalence,

bone mineral density and biochemical markers may predict those of are at greatest risk for fracture.

3.3 Radiological Assessment

Distinctive features of corticosteroid-induced osteoporosis can be seen on x-ray.[40] In postmenopausal osteoporosis, horizontal trabeculae are lost out of proportion to vertical trabeculae, leading to a 'corduroy stripe' appearance;[1] however, in corticosteroid-induced osteoporosis, vertical and horizontal trabeculae are equally thin, producing a uniformly translucent appearance of the vertebrae. Abundant pseudocallus formation at the site of stress fractures is a hallmark of corticosteroid-induced osteoporosis.[1] This formation is most frequently seen at the end plates of collapsed vertebrae or around stress fractures in the ribs or pelvis. The basis for this is a reduction in osteoblastic activity and increased production of cartilaginous callus that becomes highly mineralised in an amorphous fashion. One should remember that x-rays cannot be used to assess corticosteroid-induced bone loss of osteoporosis because of their low sensitivity and specificity. On the other hand, the presence of a vertebral fracture at baseline or any time throughout corticosteroid therapy identifies those who are at greatest risk for subsequent fractures.

3.4 Bone Density Assessment

Trabecular bone loss occurs early in the course of corticosteroid therapy, although both trabecular and cortical loss occur over time. Early changes in bone mineral density can be detected in the lumbar spine and femoral neck by use of dual x-ray energy absorptiometry or quantitative computed tomography.[108] Bone loss is identifiable by 6 months with dual energy x-ray absorptiometry and, on average, 5% of bone mass is lost within the first year of therapy. During the second and third years of treatment, bone loss continues to occur particularly at the femoral neck, but at a slower rate.[33]

Bone mineral density measurements have been used to assess the risk of osteoporosis and fractures in corticosteroid-treated patients. While these measurements are accurate and precise, they may underestimate the fracture risk in patients receiving corticosteroids. With the use of these drugs, bone strength may not be related to bone mass as directly as it is in primary osteoporosis. For instance, in postmenopausal women, a decrease in bone mineral density of 1 standard deviation is associated with a 2-fold increase in fracture risk.[109] The incremental increase in fracture risk may be greater in patients who are treated with corticosteroids.[110]

4. Management of Corticosteroid-Induced Osteoporosis

4.1 General Principles

The main goal in the prevention and treatment of corticosteroid-induced bone loss is to stabilise bone mass and reduce fracture risk (fig. 1). The American College of Rheumatology (ACR) published guidelines for the prevention of glucocorticoid-induced osteoporosis. These guidelines recommend a baseline bone density before long term corticosteroid treatment, in addition to repeat measurements to assess bone loss. Treatment recommendations include calcium, vitamin D and hormone replacement therapy.[17] In addition, nonpharmacological recommendations, including smoking cessation, limitation in alcohol consumption and weight-bearing exercise, should be included.

Therapeutically, alternative therapy or early discontinuation of corticosteroids is the best means of preventing corticosteroid-induced osteoporosis, but in practice, the termination of corticosteroid therapy is often clinically difficult or impossible. Thus, care must be taken to ensure that corticosteroid therapy is truly indicated and initiated only when potential benefits outweigh potential risks. Once corticosteroid therapy is initiated, repeated follow-up is needed to ensure that the dose, duration, treatment intervals, and corticosteroid preparation and route of administration are optimised to allow for the greatest benefit-to-risk ratio.

Patients who have discontinued corticosteroid therapy exhibit a rebound increase in osteoblastic function and new bone formation.[46,87,111,112] Unfortunately, even with this increase in bone forma-

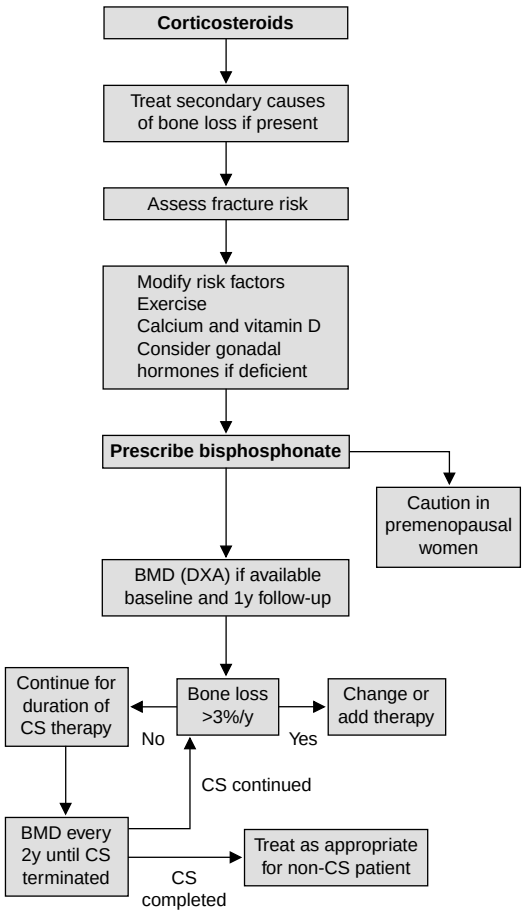

Fig. 1. An approach to the patient receiving corticosteroid therapy. **BMD** = bone mineral density; **CS** = corticosteroids; **DXA** = dual energy x-ray absorptiometry.

tion, bone resorption rates are usually greater than formation rates for some time following corticosteroid cessation. Consequently, bone loss still occurs. If corticosteroid therapy must be continued, the lowest possible dose should be used. Alternate day corticosteroid therapy may be less toxic than daily administration;[113] nonetheless, bone loss still has been detected in individuals receiving alternate day treatment.[114]

Therapies to prevent bone loss are more effective when initiated at the start of corticosteroid treatment than during treatment, when bone loss is likely to have already occurred. Several therapies are available. Primary therapies include bisphosphonates and hormone replacement therapy. Many secondary therapies exist which can be used as adjuncts or alternatives to primary therapies (if the primary therapy is contraindicated for the patient). Secondary therapies include calcitonin, fluoride, anabolic therapy, calcium and vitamin D, and thiazide diuretics.

4.2 Bisphosphonates

Bisphosphonates are potent inhibitors of bone resorption. Clinical trials in postmenopausal women with established osteoporosis have provided conclusive evidence that therapy with this class of drug leads to significant improvement in bone mass[115-117] and a reduction in subsequent fractures.[118-120]

Although differences exist between the pathogenesis of postmenopausal osteoporosis and corticosteroid-induced osteoporosis, both exhibit increased bone resorption. This being the case, it might be expected that bisphosphonates may have an important role in preventing bone loss and treating established bone loss in patients on long term corticosteroid therapy. Substantial data support the use of bisphosphonates in corticosteroid-induced osteoporosis. Indeed, in a recent meta-analysis that examined calcitonin, vitamin D, fluoride and bisphosphonates in corticosteroid-treated patients, bisphosphonate therapy was found to have a larger bone density treatment effect at the lumbar spine than either calcitonin or vitamin D.[121]

18 randomised, controlled clinical trials,[122-139] 11 prevention and 7 treatment, have been identified in which the efficacy of bisphosphonates has been evaluated in corticosteroid-treated patients. In general, patients had a variety of underlying diseases that required corticosteroid therapy; for the most part, all patients were given calcium and/or vitamin D supplements throughout the study (table I).

Of the prevention studies,[122-135] 6 examined etidronic acid, and 1 study each examined alendronic acid, clodronic acid and intravenous pami-

Table I. Summary of data from randomised trials of various biphosphonate drugs in the prevention or treatment of osteoporosis

Reference	Study design (duration)	No. of patients (M/F)	Corticosteroid duration at entry	Drug investigated	Lumbar spine BMD (% change from baseline)			Femoral neck BMD (% change from baseline)		
					drug treatment group	Placebo group	difference	drug treatment group	placebo group	difference
Prevention trials										
Adachi et al.[123]	rct (1y)	141 (54/87)	<100 days	ETA	0.6	–3.2	3.8†	0.2	–1.7	1.9
Roux et al.[122]	rct (1y)	117 (42/75)	<90 days	ETA	0.3*	–2.8*	3.1†	–1.3*	–2.6*	1.3
Mulder & Struys[127]	pcs (1y)	20 (0/20)	At baseline	ETA	1.4*	–5.0*	6.4†	NR	NR	NR
Wolfhagen et al.[124]	rct (1y)	12 (3/9)	<1mo	ETA	0.4	–3.0*	3.4†	–0.1	–1.5	1.4
Jenkins et al.[125]	rct (1y)	28	At baseline	ETA	1.8	–3.7	5.5†	NR	NR	NR
Skingle & Crisp[126]	rct (2y)	55 (11/44)	At baseline	ETA	4.8*	–0.7	5.51†	NR	NR	NR
Boutsen et al.[129]	rct (1y)	27 (5/22)	At baseline	PMA	3.9	–6	9.9	3	–4.1	7.1
Nordborg et al.[131]a	rct (1y)	27 (6/21)	At baseline	CLA	NR	NR	NR	1.0	2.0	–1.0
Gonnelli et al.[130]b	rct (1y)	30 (10/20)	At baseline	ALA	0.8	–4.5	5.3†	NR	NR	NR
Cohen et al.[128]	rct (1y)	30 (10/20)	<3mo	RSA	0.6	–2.8*	3.4†	0.8	–3.1	3.9†
Treatment trials										
Pitt et al.[133]	rct (2y)	49 (19/30)	>6mo	ETA	5.1*	1.0	4.1†	2.5	3.6*	–1.1
Guesens et al.[134]	rct (2y)	37 (0/37)	>3mo	ETA	4.9*	–2.4	7.3†	3.6*	–2.4	6.0
Worth et al.[135]	rct (6mo)	33 (12/21)	>9mo	ETA	5.0*	–4.3*	9.3†	NR	NR	NR
Reid et al.[139]c	rct (1y)	35 (19/16)		PMA	19.6*	–8.8	28.4†	NR	NR	NR
Saag et al.[136]	rct (1y)	477 (141/336)	Stratified	ALA	2.9*	–0.4	3.3†	1.0*	–1.2*	2.2†
Saag et al.[137]	rct (2y)	208	Stratified	ALA	3.9*	–0.8	4.7†	0.6	–2.9*	3.5†
Reid et al.[138]	rct (1y)	290	>6mo	RSA	2.9*	0.4	2.5†	1.8*	–0.3	2.1†

a BMD – whole body.

b BMD – distal radius.

c BMD – computed tomography of lumbar spine.

ALA = alendronic acid; **BMD** = bone mineral density; **CLA** = clodronic acid; **ETA** = etidronic acid; **F** = female; **M** = male; **NR** = not reported; **pcs** = prospective cohort study; **PMA** = pamidronic acid; **rct** = randomised controlled trial; **RSA** = risedronic acid; * = $p < 0.05$ *vs* baseline; † = $p < 0.05$ between groups.

dronic acid. Two studied risedronic acid, 1 examining the recommended 5mg dose, the other the 2.5mg dose and a cyclical dose of 15mg for 2 weeks out of every 15 weeks. Bisphosphonate therapy resulted in slight increases in lumbar spine bone mineral density, whereas treatment with placebo resulted in bone loss. Five studies report data on the femoral neck.[122-124,128,129,135] Bisphosphonate-treated patients were found to have small increases in femoral neck bone mineral density, while decreases were observed in recipients of placebo. Among these, the risedronic acid 5mg study found a significant difference between treatment groups.[128] Two studies evaluated radial bone mineral density.[123,130] One study indicated that placebo recipients significantly lost more bone mass than the alendronic acid-treated group.[130] In the etidronic acid study, bone mineral density was maintained in both groups.[123]

Of the 7 treatment studies,[133-139] 3 examined etidronic acid, 2 alendronic acid, 1 risedronic acid and 1 pamidronic acid. In the studies, lumbar spine bone mineral density increased from baseline in the bisphosphonate groups, whereas it decreased, for the most part, in the placebo groups after therapy. In all 7 trials, differences between bisphosphonate and placebo groups were statistically significant. Five studies reported data on the femoral neck.[132,134,136-138] Of these, the 3 largest studies found significant differences between the treatment groups, in favour of bisphosphonate therapy.[136-138] Furthermore, pooled results from the alendronic acid trials demonstrated significant differences between groups in trochanter bone mineral density in favour of alendronic acid-treated patients after 1[136] and 2[137] years of treatment.

Ideally, bisphosphonates should protect patients from skeletal fractures. Nine studies identified incident fractures.[122,123,129,133-138] Four trials found a reduced vertebral fracture incidence with bisphosphonate therapy. Among the postmenopausal women in the cyclical etidronic acid study of Adachi et al.,[123,140] etidronic acid-treated postmenopausal women experienced an 85% reduction in the proportion of patients with vertebral fractures, compared with the placebo group. The relative risk for fracture in all patients within the etidronic acid group as compared with the placebo group was 0.6 [95% confidence interval (CI) 0.2 to 1.6]. In the study by Saag et al.,[137] new vertebral fractures were uncommon. The majority of new fractures occurred among postmenopausal women. Overall, there was a trend to fewer vertebral fractures in the pooled alendronic acid-treated group (incidence of new vertebral fractures 2.3 *vs* 3.7% in the placebo group; relative risk 0.6, 95% CI 0.1 to 4.4).[134] In the other 2 studies, significantly fewer incident vertebral fractures were sustained in patients who were treated with either alendronic acid[137] or risedronic acid.[138]

Bisphosphonate treatment consistently improves axial bone mineral density in corticosteroid-treated patients, with a smaller detectable benefit to the appendicular skeleton. The patient populations studied to date have, of practical necessity, been heterogeneous as to morbidity, corticosteroid dose and duration, and initial skeletal status. Treatment of established corticosteroid-induced bone loss results in restoration of lumbar spine bone mineral density at least as effectively (if not more so) as the use of bisphosphonates for primary prevention. Cyclical etidronic acid, alendronic acid and risedronic acid therapies may well reduce incident vertebral fractures in patients treated with corticosteroids. Clodronic acid and pamidronic acid have been studied less frequently, and thus it is difficult to weigh their efficacy against either cyclical etidronic acid or alendronic acid. In future, the results of comparison trials may help determine the role of specific bisphosphonates in the treatment and prevention of corticosteroid-induced osteoporosis.

4.3 Hormone Replacement Therapy

Two intervention studies have been performed evaluating hormone replacement therapy in the treatment of corticosteroid-induced osteoporosis.[141,142] One of these was retrospectively controlled, and as such it was not included.[141] In these studies, the patients were postmenopausal women

with either rheumatoid arthritis or asthma. In one study, calcium supplements were given to bring the total intake to 1500 mg/day,[141] whereas in the other study, calcium supplements (400 mg/day) were given to all patients.[142] The average age of the patients ranged from 56 to 68 years. No primary prevention studies have been completed.

The results of the studies indicated that mean bone mineral density of the lumbar spine increased in the hormone replacement treatment groups, whereas it decreased in the placebo groups after therapy. The differences between treatment groups were significant. One study described data for femoral neck bone mineral density.[142] A nonsignificant difference was found between treatment groups.

The use of selective estrogen receptor modulators in the prevention of coricosteroid-induced osteoporosis may be of benefit. In a study of patients with breast cancer, tamoxifen was given to women with or without additional therapy with prednisolone. There was a mean gain of 0.46% in the tamoxifen group and 1.95% in those given additional prednisolone. Thus, the predicted corticosteroid-induced bone loss was inhibited by tamoxifen.[143]

In summary, hormone replacement therapy exhibited a positive effect on bone mineral density in the treatment of corticosteroid-induced osteoporosis. Although selective estrogen receptor modulator therapy such as raloxifene has been shown to be effective in the treatment of postmenopausal osteoporosis,[144] further research is needed to elucidate its role in the management of corticosteroid-induced osteoporosis.

4.4 Calcitonin

Seven randomised, placebo-controlled trials have assessed the efficacy of calcitonin in corticosteroid-induced osteoporosis.[145-151] In these studies, calcitonin was administered intranasally or subcutaneously. On average, the studies have been relatively small. Most patients in these studies have had pulmonary disease, rheumatological disorders or vasculitis, although small numbers of patients with various other underlying conditions have also been studied. Patients were middle-aged to elderly (mean age 49 to 72 years).

Of the 7 trials, 3 were prevention trials.[144-147] The results demonstrated that lumbar spine bone mineral density decreased from baseline in both treatment groups, but to a lesser extent in the calcitonin-treated than in the placebo groups. Findings from 1 study indicated that differences between groups were significant after therapy.[145] In the other 2 studies,[146,147] calcitonin did not provide statistically greater bone preservation than placebo. Bone mineral density data on femoral neck, trochanter, Ward's triangle, distal radius and whole body have also been described. No significant differences were found between treatment groups at these sites following therapy.

Four treatment trials have been conducted.[148-151] Three of these measured lumbar spine bone mineral density.[148-150] After therapy, lumbar spine bone mineral density increased from baseline in the active treatment groups, whereas it decreased in the placebo groups. Two studies demonstrated significant differences between treatment groups after therapy.[149,150] Data on distal radius[151] and femoral neck[148] have also been reported. In these studies, bone mineral density increased in the calcitonin groups and decreased in the placebo groups after therapy. At both sites, the differences between groups were significant.

Five studies evaluated fracture rates.[146-149,151] No significant differences in fracture rates were found between treatment groups. This may reflect the small sample sizes of the studies and, thus, the lack of power to detect differences between treatment groups.

Adverse effects were common in corticosteroid-treated patients given subcutaneous calcitonin.[150,151] One study found that 23% of those receiving calcitonin withdrew because of adverse effects.[150] It was also difficult to recruit individuals to these studies because of the need to inject medication.[146] Intranasal calcitonin has greater patient acceptance, and the adverse effects are less severe and much less common.[145,147-149] While the nasal formulation was better tolerated than the injectable preparation,

the positive effects on bone mineral were about half that seen with the latter agent.

One of the potential additional benefits of calcitonin beyond improving bone mass is that it may relieve pain associated with vertebral fracture. Ringe and Welzel[151] found that the amount of pain experienced by those treated with calcitonin (100IU subcutaneously every 2 days) was significantly less than in the placebo group, and the difference persisted for the duration of the study. No attempt was made to delineate the underlying origins of pain or to correlate the pain with new vertebral fractures.

In summary, studies of calcitonin efficacy in corticosteroid-induced osteoporosis suggest that this drug, whether subcutaneous or intranasal, produces a beneficial effect on bone density. This appears to be true in the prevention of corticosteroid-induced osteoporosis as well as its treatment. The benefit may be evident at 6 months, but is most readily seen at 1 year. The most consistent positive changes are seen in the spine. Studies with greater patient populations will be necessary to prove a reduction in fracture risk.

4.5 Fluoride

Since corticosteroids suppress osteoblastic activity, drugs that may reverse this complication should be useful. Four intervention studies have been performed assessing fluoride therapy in the treatment of corticosteroid-induced osteoporosis.[151-155] The studies used either sodium fluoride or monofluorophosphate. One trial compared the advantage of adding sodium fluoride to cyclical etidronic acid therapy.[153] Patients in the above studies had various underlying conditions that required corticosteroid therapy. In general, similar effects were seen with either sodium fluoride or monofluorophosphate. Patients were, for the most part, middle-aged (mean age 45 to 60 years). No primary prevention studies have been completed.

On average, vertebral bone mineral density substantially increased in fluoride-treated patients after 18 to 24 months of therapy, whereas it remained stable or slightly increased from baseline in the placebo-treated patients. Differences between treatment groups were significant after therapy. Three studies report data for femoral neck.[152,153,155] These found that femoral neck bone mineral density decreased from baseline in both treatment and placebo groups. Except in 1 study,[153] the loss of femoral neck bone mineral density was greater in fluoride-treated patients than in patients in the placebo groups. All trials assessed vertebral fracture rates. However, none had enough power to demonstrate an effect on vertebral fracture rates. In addition, while fluoride increases bone mineral density, there is the concern that it might decrease the mechanical competence of bone and therefore might increase the number of peripheral fractures.

In summary, fluoride seems to increase bone mineral density at the spine without protecting the hip from the effects of corticosteroids. There may be an added benefit for the spine in using fluoride in combination with an antiresorptive agent, but no benefit has been seen in the appendicular skeleton and concerns about an increase in peripheral fracture rates have been expressed. Fluoride therapy has not been shown to prevent fractures in corticosteroid-induced osteoporosis.

4.6 Anabolic Therapy

Three randomised, controlled studies have used anabolic therapy in the treatment of corticosteroid-induced osteoporosis.[156-158] One study each examined human parathyroid hormone, testosterone and nandrolone decanoate. The testosterone trial enrolled men, whereas the other 2 trials enrolled postmenopausal women. In these studies, all of the men had asthma and postmenopausal women predominantly had rheumatoid arthritis. All hypogonadal men were given calcium supplements (1000 mg/day), whereas postmenopausal women received 1200 to 1500 mg/day calcium and 600 to 800 IU/day of vitamin D as part of their diet and/or supplement. In the parathyroid hormone study, all women were receiving concomitant hormone replacement therapy. The average age of the patients ranged from 54 to 65 years. No primary prevention studies have been completed.

The results of the studies indicated that bone mineral density of the lumbar spine[156-158] and forearm[159] increased in the treatment groups, whereas it decreased in the placebo groups after therapy. The differences between groups were significant. Human parathyroid hormone was found to have no effect on femoral neck, trochanter, total hip and distal radius bone mineral density during the first year of therapy.[156] However, during the second year of follow-up, after discontinuation of human parathyroid hormone therapy, significant increases in lumbar spine, total hip and femoral neck bone mineral density were demonstrated.[157] Testosterone therapy was found to have no effect on whole body bone mineral density following therapy.[158]

In summary, anabolic therapy may have some benefit in the treatment of corticosteroid-induced bone loss. The prevention of corticosteroid-induced osteoporosis with these agents still needs to be determined.

4.7 Calcium and Vitamin D and its Analogues

There are no randomised, controlled trials of calcium alone in the prevention or treatment of corticosteroid-induced osteoporosis. However, 6 controlled studies have been identified that examined the effects of vitamin D or its analogues in corticosteroid-treated patients.[147,160-165] In these studies, patients in the active treatment groups received calcium supplements ranging from 500 to 1000 mg/day. Calcium supplements were administered to patients in the placebo groups in 3 studies.[147,158,164] In the other trials, no medication was given in the placebo groups. Patients predominantly required corticosteroid therapy because of rheumatological disorders. Generally, middle-aged patients were studied (mean age 36 to 55 years), although in 1 study, elderly patients were investigated (mean age >63 years).[160]

Of the 7 studies, 3 were prevention studies,[147,160,165] one evaluating calcitriol[147], one alfacalcidol[165] and the other vitamin D.[160] The results of the 3 trials indicated that lumbar spine bone mineral density decreased from baseline in both treatment groups, but to a lesser extent in the active treatment groups than in the placebo groups. In the vitamin D trial, the differences between groups were not significant after therapy, whereas in the active vitamin D metabolites, alfacalcidol and calcitriol trials, significant differences between groups were noted. The calcitriol study also assessed data on the femoral neck and distal radius. At these skeletal sites, no significant differences were found between the treatment groups and placebo (calcium alone).

The 4 treatment studies[161-164] were relatively small. Of these, 3 examined vitamin D and 1 calcitriol. Findings were that lumbar spine bone mineral density increased from baseline in the active treatment groups in all 4 studies, whereas it decreased in the placebo group in 1 trial following therapy. One study demonstrated a significant difference in lumbar spine bone mineral density between the treatment groups.[161] This study also demonstrated significant differences between treatment groups in trochanter bone mineral density, in favour of vitamin D therapy.

One treatment and both prevention studies evaluated fracture rates.[142,155,159] In these studies, all patients had spinal x-rays. No significant differences in fracture rates were found between groups after therapy. Indeed, in 1 study[164] fractures were frequently reported in both treatment groups.

Although most studies investigating vitamin D treatment did not report adverse effects associated with therapy, the few studies that did frequently reported hypercalciuria. Because adverse effects may occur, urinary calcium levels should be checked before instituting therapy and they should be monitored every 3 months while taking vitamin D. Serum calcium should also be monitored regularly, and if hypercalcaemia develops, the calcium or vitamin D metabolite dose should be reduced appropriately.

In summary, while it is likely that vitamin D and its analogues have some benefit in the prevention of corticosteroid-induced osteoporosis, it is quite clear that these agents cannot completely prevent corticosteroid-induced bone loss. Nonetheless, vi-

tamin D therapy has been shown to maintain spine and hip bone mineral density in patients who are receiving long term corticosteroid therapy. The meta-analysis by Amin et al.[121] demonstrated a moderate bone density effect compared with no therapy or calcium and that effect of treatment was similar in efficacy to calcitonin.

4.8 Thiazide Diuretics

Thiazides or other calcium-retaining diuretics have not been evaluated in prospective, randomised, controlled trials using bone mineral density or fracture rates as a primary outcome measure in corticosteroid-induced osteoporosis. However, 1 randomised, controlled trial of a thiazide-like diuretic (chlorthalidone) in the treatment of hypertension showed a beneficial effect on bone density in postmenopausal osteoporosis.[166]

The major effect of thiazide diuretic administration is to reduce calcium excretion via increased tubular calcium reabsorption in the distal tubule. One study demonstrated that 50mg of hydrochlorothiazide given twice daily also increased intestinal calcium absorption in corticosteroid-treated patients.[79] Nonetheless, thiazide diuretics are not without risk; for example, they may aggravate hypokalaemia in corticosteroid-treated patients.[167] In addition, there is a risk of hypercalcaemia developing in patients treated with a combination of vitamin D and thiazides;[168] therefore, serum calcium levels should be carefully monitored. Despite their apparent widespread use, there is a lack of clinical data with appropriate long term outcome measures supporting the use of thiazide diuretics in corticosteroid-induced osteoporosis.

5. Summary of Therapeutic Options

Based on currently available data, bisphosphonates appear to be the drugs of choice for the prevention and/or treatment of corticosteroid-induced osteoporosis. In fact, the data for the bisphosphonates are more compelling than for any other agent. While hormone replacement therapy is extensively used in the treatment of primary osteoporosis, data concerning its effectiveness when used alone in corticosteroid-induced osteoporosis are limited. If bisphosphonate therapy is contraindicated, calcitonin may be an effective alternative, particularly in those with acute back pain secondary to vertebral fractures. For patients who have been treated but continue to lose bone, fluoride and anabolic therapy should be considered. Although vitamin D and its analogues appear to have weak positive effects on bone in those receiving corticosteroids, they may not be sufficiently potent to be used alone. As such, these agents should be administered in combination with other medications. Currently, little evidence is available to support the use of thiazide diuretics. In future, the results of long term clinical and comparison trials may provide us with more definitive treatment strategies.

References

1. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. Ann Intern Med 1990; 112: 352-64
2. Ruegsegger P, Medici TC, Ankiler M. Corticosteroid-induced bone loss. A longitudinal study of alternate day therapy in patients with bronchial asthma using quantitative computer tomography. Eur J Clin Pharmacol 1983; 25: 615-20
3. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. Ann Rheum Dis 1995; 54: 49-52
4. Hooyman JR, Melton III JL, Nelson AM, et al. Fractures after rheumatoid arthritis. Arthritis Rheum 1984; 27: 1353-61
5. Sambrook PN, Birmingham J, Kempler S, et al. Corticosteroid effects on proximal femur bone loss. J Bone Miner Res 1990; 5: 1211-6
6. Baylink DJ. Glucocorticoid-induced osteoporosis. N Engl J Med 1983; 309: 306-8
7. Adinoff AD, Hollister JR. Steroid-induced fractures and bone loss in patients with asthma. N Engl J Med 1983; 309: 265-8
8. Kanis JA, Pitt FA. Epidemiology of osteoporosis. Bone 1992; 13 Suppl. 1: S7-15
9. Cushing H. The basophil adenomas of the pituitary body and their clinical manifestations. Bull Johns Hopkins Hosp 1932; 50: 137-95
10. Manolagas SC, Weinstein RS. New developments in the pathogenesis and treatment of steroid-induced osteoporosis. J Bone Miner Res 1999; 14: 1061-6
11. Buckley LM, Marquez M, Feezor R, et al. Prevention of corticosteroid-induced osteoporosis: results of a patient survey. Arthritis Rheum 1999; 42: 1736-9
12. 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: 271-92
13. Adachi JD, Olszynski W, Hanley D, et al. Management of corticosteroid-Induced osteoporosis. Semin Arthritis Rheum 2000; 29: 228-51

14. Adachi JD, Ioannidis G. Glucocorticoid-induced osteoporosis. Drug Dev Res 2000; 49: 120-34
15. Miller PD, Bonnick SL, Rosen CJ, for the Society for Clinical Densitometry. Clinical utility of bone mass measurements in adults: consensus of an international panel. Semin Arthritis Rheum 1996; 25: 361-72
16. Patel S. Current and potential future drug treatment for osteoporosis. Ann Rheum Dis 1996; 55: 700-14
17. American College of Rheumatology Task Force on Osteoporosis Guidelines. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum 1996; 39: 1791-801
18. Gulko PS, Mulloy AL. Glucocorticoid-induced osteoporosis: pathogenesis, prevention and treatment. Clin Exp Rheumatol 1996; 14: 199-206
19. Dequeker J, Westhovens R. Low dose corticosteroid associated osteoporosis in rheumatoid arthritis and its prophylaxis and treatment: bones of contention. J Rheumatol 1995; 22: 1013-9
20. Lane NE, Mroczkowski PJ, Hochberg MC. Prevention and management of glucocorticoid-induced osteoporosis. Bull Rheum Dis 1995; 44: 1-4
21. Eastell R. Management of corticosteroid-induced osteoporosis. UK Consensus Group Meeting on Osteoporosis. J Intern Med 1995; 237: 439-47
22. Sambrook PN, Jones G. Corticosteroid osteoporosis. Br J Rheumatol 1995; 34: 8-12
23. Joseph JC. Corticosteroid-induced osteoporosis. Am J Hosp Pharm 1994; 51: 188-97
24. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis. Rheum Dis Clin North Am 1994; 20: 630-51
25. Reid IR, Grey AB. Corticosteroid osteoporosis. Baillieres Clin Rheumatol 1993; 7: 573-87
26. Olbricht T, Benker G. Glucocorticoid-induced osteoporosis: pathogenesis, prevention and treatment with special regard to the rheumatic diseases. J Intern Med 1993; 234: 237-44
27. Hahn TJ. Steroid and drug-induced osteoporosis. In: Favus MJ, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. 2nd ed. New York (NY): Raven Press, 1993: 250-5
28. Adachi JD, Bensen WG, Hodsman AB. Corticosteroid-induced osteoporosis. Semin Arthritis Rheum 1993; 22: 375-84
29. Libanati CR, Baylink DJ. Prevention and treatment of glucocorticoid-induced osteoporosis: a pathogenetic perspective. Chest 1992; 102: 1426-35
30. Smith R. Corticosteroids and osteoporosis. Thorax 1990; 45: 537-8
31. Mitchell DR, Lyles KW. Glucocorticoid-induced osteoporosis: mechanisms for bone loss; evaluation of strategies for prevention. J Gerontol 1990; 45: M153-5
32. Saito JK, Davis JW, Wasnich RD, et al. Users of low-dose glucocorticoids have increased bone loss rates: a longitudinal study. Calcif Tissue Int 1995; 57: 115-9
33. Adachi JD, Bensen WG, Bell MJ, et al. Corticosteroid induced osteoporosis: follow-up over 3 years. In: Christiansen C, Overgaard K, editors. Osteoporosis 1990 (3), Third International Symposium on Osteoporosis. Copenhagen: Osteopress ApS, 1990: 1745-7
34. Picado C, Luengo M. Corticosteroid-induced bone loss: prevention and management. Drug Saf 1996; 15: 347-59
35. Soucy E, Bellamy N, Adachi JD, et al. A Canadian survey on the management of corticosteroid induced osteoporosis by rheumatologists. J Rheum 2000; 27: 1506-12
36. Verstraeten A, Dequeker J. Vertebral and peripheral bone mineral content and fracture incidence in postmenopausal patients with rheumatoid arthritis: effect of low dose corticosteroids. Ann Rheum Dis 1986; 45: 852-7
37. Gough AK, Lilley J, Eyre S, et al. Generalized bone loss in patients with early rheumatoid arthritis. Lancet 1994; 344: 23-7
38. Gennari C. Glucocorticoids and bone. In: Peck WA, editor. Bone and mineral research/3. Amsterdam: Elsevier, 1985: 213-32
39. Hahn TH, Boiseau VC, Avioli LV. Effect of chronic corticosteroid administration on diaphyseal and metaphyseal bone mass. J Clin Endocrinol Metab 1974; 39: 274-82
40. Maldague B, Malghem J, de Deauxchaisnes CN. Radiologic aspects of glucocorticoid-induced bone disease. Adv Exp Med Biol 1984; 171: 155-90
41. Pearce G, Tabensky DA, Delmas PD, et al. Corticosteroid-induced bone loss in men. J Clin Endocrinol Metab 1998; 83: 801-6
42. Aman S, Hakala M, Silvennoinen J, et al. Low incidence of osteoporosis in a two year follow-up of early community based patients with rheumatoid arthritis. Scand J Rheumatol 1998; 27: 188-93
43. Kroger H, Honkanen R, Saarikoski S, et al. Decreased axial bone mineral density in perimenopausal women with rheumatoid arthritis: a population based study. Ann Rheum Dis 1994; 53: 18-23
44. Van Staa TP, Leufkens HG, Abenhaim L, et al. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000; 15: 993-1000
45. Naganathan V, Jones G, Nash P, et al. Vertebral fracture risk with long-term corticosteroid therapy; prevalence and relation to age bone density, and corticosteroid use. Arch Intern Med 2000; 160: 2917-22
46. Bressot C, Meunier PJ, Chapuy MC, et al. Histomorphometric profile, pathophysiology, and reversibility of glucocorticoid-induced osteoporosis. Metab Bone Dis Relat Res 1979; 1: 303-11
47. Dempster DW, Arlot MA, Meunier PJ. Mean wall thickness and formation periods of trabecular bone packets in glucocortico-steroid-induced osteoporosis. Calcif Tissue Int 1983; 35: 410-7
48. Jee WSS, Park HZ, Roberts WE, et al. Glucocorticosteroid and bone. Am J Anat 1970; 129: 477-9
49. Chappard D, Legrand E, Basle MF, et al. Altered trabecular architecture induced by corticosteroids: a bone histomorphometric study. J Bone Miner Res 1996; 11: 676-85
50. Frost HM, Villaneuva AR. The effect of cortisone on lamellar osteoblastic activity. Henry Ford Hosp Med J 1961; 9: 97-101
51. Ishida Y, Heersche JNM. Glucocorticoid-induced osteoporosis: both in vivo and in vitro concentrations of glucocorticoids higher than physiological levels attenuate osteoblast differentiation. J Bone Miner Res 1998; 13: 1822-6
52. Peck WA, Brand J, Miller I. Hydrocortisone-induced inhibition of protein synthesis and uridine incorporation in isolated bone cells in vitro. Proc Natl Acad Sci USA 1967; 57: 1599-606

53. Caporali R, Gentile S, Caprotti M, et al. Serum osteocalcin (bone gla-protein) and steroid osteoporosis in rheumatoid arthritis. J Rheumatol 1991; 18: 148-9
54. Godschalk MF, Downs RW. Effect of short-term glucocorticoids on serum osteocalcin in healthy young men. J Bone Miner Res 1988; 3: 113-5
55. Neilsen HK, Thomsen K, Eriksen EF, et al. The effects of high-dose glucocorticoid administration on serum bone gamma carboxyglutamic acid-containing protein, serum alkaline phosphatase and vitamin D metabolites in normal subjects. Bone Miner 1988; 4: 105-13
56. Prummel MF, Wiersinga WM, Lips P, et al. The course of biochemical parameters of bone turnover during treatment with corticosteroids. J Clin Endocrinol Metab 1991; 72: 382-6
57. Reid IR, Chapman GE, Fraser TRC, et al. Low serum osteocalcin levels in glucocorticoid-treated asthmatics. J Clin Endocrinol Metab 1986; 62: 379-83
58. Kotowicz MA, Hall S, Hunder GG, et al. Relationship of glucocorticoid dosage to serum bone gla-protein concentration in patients with rheumatologic disorders. Arthritis Rheum 1990; 33: 1487-91
59. Stellon AJ, Webb A, Compston JE. Bone histomorphometry and structure in corticosteroid treated chronic active hepatitis. Gut 1988; 29: 378-84
60. Fucik RF, Kukreja SC, Hargis GK, et al. Effect of glucocorticoids on function of the parathyroid glands in man. J Clin Endocrinol Metab 1975; 40: 152-5
61. Lukert BP, Adams JS. Calcium and phosphorus homeostasis in man: effect of corticosteroids. Arch Intern Med 1976; 136: 1249-53
62. Hahn TJ, Hahn BH. Osteopenia in patients with rheumatic diseases: principles of diagnosis and therapy. Semin Arthritis Rheum 1976; 6: 165-88
63. Hahn TJ, Halstead LR, Teitelbaum SL, et al. Altered mineral metabolism in glucocorticoid induced osteopenia: effect of 25-hydroxyvitamin D administration. J Clin Invest 1979; 64: 655-65
64. Seeman E, Dumar R, Hundar GG, et al. Production, degradation and circulating levels of 1,25-dihydroxyvitamin D in health and chronic glucocorticoid excess. J Clin Invest 1980; 66: 664-9
65. Hahn TJ, Halstead LR, Baran DT. Effects of short-term glucocorticoid administration on intestinal calcium absorption and circulating vitamin D metabolite concentrations in man. J Clin Endocrinol Metab 1981; 52: 111-5
66. Klein RG, Arnaud SB, Gallagher JC, et al. Intestinal calcium absorption in exogenous hypercortisolism: role of 25-hydroxyvitamin D and corticosteroid dose. J Clin Invest 1977; 60: 253-9
67. Kimberg DV, Baerg RD, Gershon E, et al. Effects of cortisone treatment on the active transport of calcium by the small intestine. J Clin Invest 1973; 52: 1680-5
68. Favus MJ, Walling MW, Kimberg DV. Effects of 1,25-dihydroxycholecalciferol on intestinal calcium transport in cortisone-treated rats. J Clin Invest 1973; 52: 1680-5
69. Suzuki Y, Ichikawa Y, Saito E, et al. Importance of increased urinary calcium excretion in the development of secondary hyperparathyroidism of patients under glucocorticoid therapy. Metabolism 1983; 32: 151-6
70. Need AG. Corticosteroids and osteoporosis. Aust NZ J Med 1987; 17: 257-72
71. Reid IR. Steroid osteoporosis. Calcif Tissue Int 1989; 45: 63-7
72. Jennings BH, Andersson KE, Johansson SA. The assessment of the systemic effects of inhaled glucocorticosteroids – the effects of inhaled budesonide vs. oral prednisolone on calcium metabolism. Eur J Clin Pharmacol 1991; 41: 11-6
73. Bikle DD, Halloran B, Fong L, et al. Elevated 1,25-dihydroxyvitamin-D levels in patients with chronic obstructive pulmonary disease treated with prednisone. J Clin Endocrinol Metab 1993; 76: 456-61
74. Williams GA, Bowser EN, Henderson WJ, et al. Calcium absorption in the rat in relation to excessive vitamin D and cortisone. Proc Soc Exp Bio Med 1960; 5: 354-8
75. Hahn TJ, Hastead LR, Strates B, et al. Comparison of subacute effects of oxazacort and prednisone on mineral metabolism in man. Calcif Tissue Int 1980; 31: 109-15
76. Lekkerkerker JF, Van Woudenberg F, Doorenbos HD. Influence of low dose of sterol therapy on calcium absorption. Acta Endocrinol (Copenh) 1972; 69: 488-96
77. Sjoberg HE. Retention of orally administered 47-calcium in man under normal diseased conditions studies with a whole-body counter technique. Acta Med Scand 1970; 509 (Suppl.): 1-28
78. Lindgren U, Lindholm S, Sarby B. Short-term effects of 1-alpha-hydroxy-vitamin D_3 in patients on corticosteroid treatment and in patients with senile osteoporosis. Acta Med Scand 1978; 204: 89-92
79. Adams JS, Wahl TO, Lukert BP. Effects of hydrochlorothiazide and dietary sodium restriction on calcium metabolism in corticosteroid treated patients. Metabolism 1981; 30: 217-21
80. Findling JW, Adams ND, Lemann J, et al. Vitamin D metabolites and parathyroid hormone in Cushing's syndrome: relationship to calcium and phosphorus homeostasis. J Clin Endocrinol Metab 1982; 52: 1680-5
81. Lee DB. Unanticipated stimulatory action of glucocorticoids on epithelial calcium absorption. Effect of dexamethasone on rat distal colon. J Clin Invest 1983; 71: 322-8
82. Binder HJ. Effect of dexamethasone on electrolyte transport in the large intestine of the rat. Gastroenterology 1978; 75: 212-7
83. Ferretti JL, Bazan JL, Alloatti D, et al. The intestinal handling of calcium by the rat in vivo, as affected by cortisol. Effect of dietary calcium supplements. Calcif Tissue Res 1978; 251: 1-6
84. Hahn TJ, Halstead LR, Haddad Jr JG. Serum 25-hydroxyvitamin D concentrations in patients receiving chronic corticosteroid therapy. J Lab Clin Med 1977; 90: 399-404
85. Chesney RW, Hamstra AJ, Mazess RB, et al. Reduction of serum 1,25-dihydroxyvitamin D_3 in Children receiving glucocorticoids. Lancet 1978; II: 1123-5
86. Godschalk M, Levy J, Downs RW. Glucocorticoids decrease vitamin D receptor numbers and gene expression in human osteosarcoma cells. J Bone Miner Res 1992; 7: 21-7
87. Sakakura M, Takebe K, Nakagawa S. Inhibition of luteinizing hormone secretion induced by synthetic LRH by long-term treatment with glucocorticoids in human subjects. J Clin Endocrinol Metab 1975; 40: 774-9

88. Luton JP, Thieblot P, Valcke JC, et al. Reversible gonadotrophin deficiency in male Cushing's disease. J Clin Endocrinol Metab 1977; 45: 488-95
89. Hsueh AJ, Erickson GF. Glucocorticoid inhibition of FSH-induced estrogen production in cultured rat granulosa cells. Steroids 1978; 32: 639-48
90. Doerr P, Pirke KM. Cortisol-induced suppression of plasma testosterone in normal adult males. J Clin Endocrinol Metab 1976; 43: 622-9
91. Schaison G, Durand F, Mowszowicz I. Effect of glucocorticoids on plasma testosterone in men. Acta Endocrinol (Copenh) 1987; 89: 126-31
92. MacAdams MR, White RH, Chipps BE. Reduction of serum testosterone levels during chronic glucocorticoid therapy. Ann Intern Med 1986; 104: 648-51
93. Montecucco C, Caporalli R, Caprotti R, et al. Sex hormones and bone metabolism in postmenopausal rheumatoid arthritis treated with two different glucocorticoids. J Rheumatol 1992; 19: 1895-990
94. Goulding A, Gold E. Effects of chronic prednisolone treatment on bone resorption and bone composition in intact and ovariectomized rats and in ovariectomized rats receiving B-estradiol. Endocrinology 1988; 122: 482-7
95. Flicker L, Hooper JL, Rodgers L, et al. Bone density determinants in elderly women: a twin study. J Bone Miner Res 1995; 10: 1607-13
96. Arden NK, Baker J, Hogg C, et al. The heritability of bone mineral density, ultrasound of the calcaneus and hip axis length: a study of postmenopausal twins. J Bone Miner Res 1996; 11: 530-4
97. Morrison D, Capewll S, Reynolds SP, et al. Testosterone levels during systemic and inhaled corticosteroid therapy. Respir Med 1994; 88: 659-63
98. Ross PD, Davis JW, Epstein RS, et al. Pre-existing fractures and bone mass predict vertebral fracture incidence in women. Ann Intern Med 1991; 114: 919-23
99. Kimble RB. Alcohol, cytokines, and estrogen in the control of bone remodeling. Alcohol Clin Exp Res 1997; 21: 385-91
100. Klein FR. Alcohol-induced bone disease: impact of ethanol on osteoblast proliferation. Alcohol Clin Exp Res 1997; 21: 392-9
101. Ernst E. Exercises for female osteoporosis: a systematic review of randomized clinical trials. Sports Med 1998; 25: 359-68
102. Kano K. Relationship between exercise and bone mineral density amoung over 5,000 women aged 40 years and above. J Epidemiol 1998; 8: 28-32
103. Egger P, Duggleby S, Hobbs R, et al. Cigarette smoking and bone mineral density in the elderly. J Epidemiol Commun Health 1996; 50: 47-50
104. Law MR, Cheng R, Hackshaw AK, et al. Cigarette smoking, sex hormones and bone density in women. Eur J Epidemiol 1997; 13: 553-8
105. Nielsen HK, Charles P, Moskelide L. The effect of single oral doses of prednisone on the circadian rhythm of serum osteocalcin in normal subjects. J Clin Endocrinol Metab 1988; 67: 1025-30
106. Need AG, Philcox JC, Hartley TF, et al. Calcium metabolism and osteoporosis in corticosteroid-treated postmenopausal women. Aust NZ J Med 1986; 16: 341-6
107. Garnero P, Weichung JS, Gineyts E, et al. Comparison of new biochemical markers of bone turnover in late postmenopausal osteoporotic women in response to alendronate treatment. J Clin Endocrinol Metab 1994; 79: 1693-700
108. Seeman E, Wagner HW, Offord KP, et al. Differential effects of endocrine dysfunction on the axial and appendicular skeleton. J Clin Invest 1982; 69: 1302-9
109. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporosis fractures. BMJ 1996; 312: 1254-9
110. Luengo M, Picado C, Rio LD, et al. Vertebral fractures in steroid dependent asthma and involutional osteoporosis: a comparative study. Thorax 1991; 46: 803-6
111. Hough S, Teitelbaum SL, Bergfeld MA, et al. Isolated skeletal involvement in Cushing's syndrome: response to therapy. J Clin Endocrinol Metab 1981; 52: 1033-8
112. Riggs BL, Jowsey J, Kelly PJ. Quantitative microradiographic study of bone remodelling in Cushing's syndrome. Metabolism 1966; 15: 773-80
113. Sheagren JN, Jowsey J, Bird DC, et al. Effect on bone growth of daily versus alternate day corticosteroid administration: an experimental study. J Lab Clin Med 1977; 89: 120-30
114. Gluck OS, Murphy WA, Hahn TJ, et al. Bone loss in adults receiving alternate day glucocorticoid therapy. Arthritis Rheum 1981; 24: 892-8
115. Tucci JR, Tonino RP, Emkey RD. Effect of three years of oral alendronate treatment in postmenopausal women with osteoporosis. Am J Med 1996; 101: 488-501
116. Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med 1990; 323: 73-9
117. Devogelaer JP, Broll H, Correa-Rotter R, et al. Oral alendronate induces progressive increases in bone mass of the spine, hip, and total body over 3 years in postmenopausal women with osteoporosis. Bone 1996: 18: 141-50
118. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med 1995: 333: 1437-43
119. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1997; 348: 1535-41
120. Storm T, Thamsborg G, Steiniche T, et al. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990; 322: 1265-71
121. Amin S, LaValley MP, Simms RW, et al. The role of vitamin D in corticosteroid-induced osteoporosis: a meta-analytic approach. Arthritis Rheum 1999; 42: 1740-51
122. Roux C, Oriente P, Laan R, et al. Randomized trial of effect of cyclical etidronate in the prevention of corticosteroid-induced bone loss. J Clin Endocrinol Metab 1998; 83: 1128-33
123. Adachi JD, Bensen WG, Brown J, et al. Intermittent cyclical etidronate therapy in the prevention of corticosteroid-induced osteoporosis. N Engl J Med 1997; 337: 382-7
124. Wolfhagen FHJ, van Buuren HR, den Ouden JW, et al. Cyclical etidronate in the prevention of bone loss in corticosteroid-treated primary biliary cirrhosis. J Hepatol 1997; 26: 325-30
125. Jenkins EA, Walker-Bone KE, Wood A, et al. The prevention of corticosteroid induced osteoporosis with intermittent cyclical etidronate. Scand J Rheumatol 1999; 28: 152-6

126. Skingle SJ, Crisp AJ. Increased bone density in patients on steroids with etidronate. Lancet 1994; 344: 543-4
127. Mulder H, Struys A. Intermittent cyclical etidronate in the prevention of corticosteroid-induced bone loss. Br J Rheumatol 1994; 33: 348-50
128. Cohen S, Levy R, 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: 2309-18
129. Boutsen Y, Jamart J, Essenlinckx W, et al. Primary prevention of glucocorticoid-induced osteoporosis with intermittent intravenous pamidronate: a randomized trial. Calcif Tissue Int 1997; 61: 266-71
130. Gonnelli S, Rottoli P, Cepollaro C, et al. Prevention of corticosteroid-induced with alendronate in sarcoid patients. Calcif Tissue Int 1997; 61: 382-5
131. Nordborg E, Schaufelberger C, Andersson R, et al. The ineffectiveness of cyclical oral clodronate on bone mineral density in glucocorticoid-treated patients with giant cell arteritis. J Intern Med 1997; 242: 367-71
132. Eastell R, Devogelaer JP, Peel NF, et al. Prevention of bone loss with risedronate in glucocorticoid-treatment rheumatoid arthritis patients. Osteoporos Int 2000; 11: 331-7
133. Pitt P, Li F, Todd P, et al. A double blind placebo controlled study to determine the effects of intermittent cyclical etidronate on bone mineral density in patients on long term oral corticosteroid treatment. Thorax 1998; 53: 351-6
134. Guesens P, Dequeker J, Vanhoof J, et al. Cyclic etidronate increases bone density in the spine and hip of postmenopausal women receiving long term corticosteroid treatment: a double-blind, randomized placebo controlled study. Ann Rheum Dis 1998; 57: 724-7
135. Worth H, Stammen D, Keck E. Therapy of steroid-induced bone loss in adult asthmatics with calcium, vitamin D, and a diphosphonate. Am J Respir Crit Care Med 1994; 150: 394-7
136. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 1998; 339: 292-9
137. Saag KG, Emkey R, Cividino A, et al. Effects of alendronate for two years and BMD and fractures in patients receiving glucocorticoids. Bone 1998; 23; S182
138. Reid DM, Hughes RA, Laan RF, et al. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. Bone Miner Res 2000; 15: 1006-13
139. Reid IR, Alexander CJ, King AR, et al. Prevention of steroid-induced osteoporosis with (3-amino-1-hydroxypropylidene)-1, 1-bisphosphonate (APD). Lancet 1988; 23: 143-6
140. Adachi JD, Pack S, Chines AA. Intermittent etidronate and corticosteroid-induced osteoporosis. N Engl J Med 1997; 337: 1921
141. Lukert BP, Johnson BE, Robinson RG. Estrogen and progesterone replacement therapy reduces glucocorticoid-induced bone loss. J Bone Miner Res 1992; 7: 1063-9
142. Hall GM, Daniels M, Doyle DV, et al. Effect of hormone replacement therapy on bone mass in rheumatoid arthritis treated with and without steroids. Arthritis Rheum 1994; 37: 1499-504
143. Fentiman IS, Saad Z, Caleffi M, et al. Tamoxifen protects against steroid-induced bone loss. Eur J Cancer 1992; 28: 684-5
144. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med 1997; 337: 1641-7
145. Adachi JD, Bensen WG, Bell MJ, et al. Salmon calcitonin nasal spray in the prevention of corticosteroid-induced osteoporosis. Br J Rheum 1997; 36: 255-9
146. Healy JH, Paget S, 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
147. 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: 1747-52
148. Kotaniemi A, Piirainen H, Paimela L, et al. Is continuous intranasal salmon calcitonin effective in treating axial bone loss in patients with active rheumatoid arthritis receiving low dose glucocorticoid therapy? J Rheumatol 1996; 23: 1875-9
149. Luengo M, Pons F, Martinez de Osaba MJ, et al. Prevention of further bone mass loss by nasal calcitonin in patients on long term glucocorticoid therapy for asthma: a two year follow up study. Thorax 1994; 49: 1099-102
150. Luengo M, Picado C, Del Rio L, et al. Treatment of steroid-induced osteopenia with calcitonin in corticosteroid-dependent asthma. Am Rev Respir Dis 1990; 142: 104-7
151. Ringe JD, Welzel D. Salmon calcitonin in the therapy of corticosteroid-induced osteoporosis. Eur J Clin Pharmacol 1987; 33: 35-9
152. Lems WF, Jacobs JWG, Bijlsma JWJ, et al. Effect of sodium fluoride on the prevention of corticosteroid-induced osteoporosis. Osteoporos Int 1997; 7: 575-82
153. Lems WF, Jacobs JWG, Bijlsma JWJ, et al. Is addition of sodium fluoride to cyclical etidronate beneficial in the treatment of corticosteroid induced osteoporosis? Ann Rheum Dis 1997; 56: 357-63
154. Guaydier-Souquieres G, Kotzki PO, Sabatier JP, et al. In corticosteroid-treated respiratory diseases, monofluorophosphate increases lumbar bone density: a double-masked randomized study. Osteoporos Int 1996; 6: 171-7
155. Rizzoli R, Bonjour JP, Slosman DO, et al. Sodium monofluorophosphate increases vertebral bone mineral density in patients with corticosteroid-induced osteoporosis. Osteoporos Int 1995; 5: 39-46
156. Lane NE, Sanchez S, Modin GW, et al. Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. Results of a randomized controlled clinical trial. J Clin Invest 1998; 102: 1627-33
157. Lane NE, Sanchez S, Modin GW, et al. Bone mass continues to increase at the hip after parathyroid hormone treatment is discontinued in glucocorticoid-induced osteoporosis: results of a randomized controlled clinical trial. J Bone Miner Res 2000; 15: 944-51
158. Reid IR, Wattie DJ, Evans MC, et al. Testosterone therapy in glucocorticoid-treated men. Arch Intern Med 1996; 156: 1173-7

159. Adami S, Fossaluzza V, Rossini M, et al. The prevention of corticosteroid-induced osteoporosis with nandrolone decanoate. Bone Miner 1992; 15: 72-8
160. Adachi JD, Bensen WG, Bianchi F, et al. Vitamin D and calcium in the prevention of corticosteroid-induced osteoporosis: a 3 year follow-up. J Rheum 1996; 23: 995-1000
161. Buckley LM, Leib ES, Cartularo KS, et al. 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: 961-8
162. Bernstein CN, Seeger LL, Anton PA, et al. A randomized, placebo-controlled trial of calcium supplementation for decreased bone density in corticosteroid-using patients with inflammatory bowel disease: a pilot study. Aliment Pharmacol Ther 1996; 10: 777-86
163. Bijlsma JW, Raymakers JA, Mosch C, et al. Effect of oral calcium and vitamin D on glucocorticoid-induced osteopenia. Clin Exp Rheumatol 1998; 6: 113-9
164. Dykman TR, Haralson KM, Gluck OS, et al. Effect of oral 1, 25-dihydroxy vitamin D and calcium on glucocorticoid-induced osteopenia in patients with rheumatic diseases. Arthritis Rheum 1984; 27: 1336-43
165. Reginster JY, Kuntz D, Verdickt W, et al. Prophylactic use of alfacalcidol in corticosteroid-induced osteoporosis. Osteoporos Int 1999; 9: 75-81
166. Wasnich RD, Davis JW, He YF, et al. A randomized, double-masked, placebo-controlled trial of chlorthalidone and bone loss in elderly women. Osteoporos Int 1995; 5: 247-51
167. Alon U, Costanzo LS, Chan JC. Additive hypocalciuric effects of amiloride and hydrochlorothiazide in patients treated with calcitriol. Miner Electrolyte Metab 1984; 10: 379-86
168. Condon JR, Nassim JR, Dent CE, et al. Possible prevention and treatment of steroid-induced osteoporosis. Postgrad Med J 1978; 54: 249-52

Correspondence and offprints: Dr *Jonathan D. Adachi*, 501-25 Charlton Ave E., Hamilton, Ontario, L8N 1Y2, Canada.
E-mail: jd.adachi@sympatico.ca