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Diagnosis and treatment of glucocorticoid-induced osteoporosis

ABSTRACT

Glucocorticoids are a mainstay in the treatment of many diseases, including pulmonary and rheumatologic disorders. Unfortunately, as many as 90% of long-term glucocorticoid recipients lose a significant amount of bone and incur an increased risk of fractures. This paper reviews the pathophysiology, diagnosis, and treatment of glucocorticoid-induced osteoporosis.

KEY POINTS

Although bone loss increases with both the dose and duration of steroid use, a host of other factors including diet, physical activity, cigarette smoking, and even the underlying disease may contribute to the severity of the resultant osteoporosis.

Risk stratification by dual energy x-ray absorptiometry, together with markers of calcium homeostasis and gonadal steroid deficiency, can help to determine the appropriate treatment.

New drugs such as calcitriol and the bisphosphonates offer promise for preventing this potentially devastating disease.

WHEN WE THINK OF OSTEOPOROSIS, we usually think of postmenopausal women. Unfortunately, osteoporosis due to other causes (some of them iatrogenic) often goes unrecognized. The most common iatrogenic cause of osteoporosis,[1,2] and the most common cause in younger persons,[3] is long-term glucocorticoid use.

Glucocorticoid-induced osteoporosis was first recognized almost 60 years ago, and remains a common cause of fractures. Estimates of its incidence vary, from as few as 30%,[4] to as many as 90% of long-term glucocorticoid recipients. Patients with obstructive airway disease or inflammatory arthritis account for approximately half of the long-term users.[5]

Physicians can prevent a considerable amount of morbidity, loss of quality of life, and mortality by taking aggressive measures to prevent and treat glucocorticoid-induced osteoporosis. Yet, although most physicians are aware of the problem, fewer than half of patients receiving significant doses of glucocorticoids receive such preventive treatment.[6,7] (Doses of 7.5 mg or more of prednisone or its equivalent per day are considered significant, although some people develop bone loss while taking lower doses.)

NATURAL HISTORY OF BONE LOSS

The rate of glucocorticoid-induced bone loss is greatest in the first 6 to 12 months of therapy,[8] and loss is most marked in sites mostly composed of trabecular bone. During the first year, some patients lose as much as 10% to 20% of their overall bone mass, and even more at trabecular bone sites.[9] Thereafter, the rate of loss usually slows to less than 5% per year.

Persons with bone loss are prone to verte-

TABLE 1

Tests for specific abnormal processes in glucocorticoid-induced osteoporosis

ABNORMAL PROCESS	TESTS
Decreased bone formation	Serum osteocalcin level*
Increased bone resorption	Urinary N-telopeptide Urinary pyridinium cross-links
Secondary hyperparathyroidism	Intact PTH and calcium levels
Renal calcium leak	24-hour urine calcium
Secondary hypogonadism	Testosterone level (men) Menstrual history (premenopausal women)

*Not generally indicated

bral and rib fractures—30% to 35% sustain at least one vertebral fracture. In addition, the risk of all fractures is two to three times higher than in age-matched controls. The risk of hip fractures, which impose an even greater economic and personal burden, is also increased 1.5-fold.

During the early phases of rapid bone loss, glucocorticoid-induced osteoporosis is asymptomatic. By the time a patient presents with a first fracture, he or she has already lost a significant amount of bone and has a high risk of subsequent fractures. Thus, early diagnosis and aggressive treatment are crucial.

Think osteoporosis when a patient starts steroids long-term

HOW DO GLUCOCORTICOIDS CAUSE OSTEOPOROSIS?

Glucocorticoids cause accelerated osteoporosis through several interacting mechanisms that affect both systemic and local factors (TABLE 1). These factors decrease bone formation and increase bone resorption, leading to a net loss of bone mass.

Decreased bone formation

Glucocorticoids act directly on osteoblasts by activating some genes and suppressing others,[10] or indirectly by decreasing levels of insulin-like growth factor I (IGF-1)[11] by suppressing its synthesis or by modifying IGF-binding proteins. These effects decrease osteoblast proliferation, inhibit osteoblast precursor maturation, and shorten osteoblast life span, all leading to reduced bone formation—a 30% reduction in bone formation per remodeling cycle.

Increased bone resorption

Steroids also increase bone resorption, perhaps in part by inducing secondary hyperparathyroidism,[12,13] although the mechanism remains controversial. When present, hyperparathyroidism can increase the activation frequency of the bone modeling units with an increase in the amount of bone resorbed at each remodeling site. However, not all patients develop secondary hyperparathyroidism, and there is controversy regarding the percentage of patients who do develop it.[12–14]

Glucocorticoids also appear to potentiate parathyroid hormone (PTH) inhibition of collagen synthesis.

Changes in calcium balance

Underlying the development of secondary hyperparathyroidism are changes in calcium balance. Glucocorticoids decrease calcium and phosphate absorption from the intestine,[15] apparently independent of vitamin D levels. In addition, early on, they increase urinary calcium excretion by decreasing renal tubular reabsorption.[16] In general, the urinary calcium/creatinine ratio is about two times normal in steroid-treated patients, and the prevalence of hypercalciuria is around 30%.[17] Calciuria may diminish with long-term steroid use as the steroids have a more pronounced effect on gastrointestinal calcium absorption. The serum calcium level is usually normal.

Hormonal changes

Glucocorticoids have a variety of effects on sex steroid levels. They blunt the luteinizing hormone response to luteinizing hormone-releasing hormone in both men and women, leading to a decrease in estradiol and testosterone production. They also suppress secretion of adrenocorticotropic hormone, leading to reduced synthesis and release of the adrenal androgens androstenedione and dehydroepiandrosterone sulfate, as well as estrone and estradiol. These hormonal changes can further accentuate bone loss.

Patient management: Summary

START THINKING ABOUT OSTEOPOROSIS as soon as you know that a patient may need to take glucocorticoids long-term, and take steps to prevent it.

HISTORY AND PHYSICAL EXAMINATION

In the history, ask questions about factors that might accelerate bone loss or increase the risk of fracture independently of glucocorticoids: smoking, alcohol intake, sedentary lifestyle, a diet low in calcium and vitamin D, menopause. Also determine if the patient has other disease processes that could contribute to secondary osteoporosis. Review current medications for those that might affect calcium balance or bone turnover, and if possible, think about changing to medications that have a less adverse effect upon bone.

In the physical examination, focus on excluding secondary causes of bone loss and assessing skeletal changes that are already apparent. Measure the patient's standing height annually, using a wall-mounted stadiometer—a 1" loss in height is a sensitive indicator of new compression fractures. Assess physical function to determine if the patient might benefit from physical therapy to reduce the risk of falls.

LAB WORK

To help guide treatment decisions, obtain:

- A 24-hour urine collection for calcium and creatinine
- A serum measurement of intact PTH
- A free testosterone level (in men)

In addition, to exclude other secondary causes of bone loss, obtain:

- Liver function tests, serum creatinine, and blood urea nitrogen
- A complete blood count
- Serum electrolytes, especially calcium, magnesium, and phosphorus.

BASELINE BONE MINERAL DENSITY DETERMINATION BY DUAL ENERGY X-RAY ABSORPTIONMETRY (DEXA)

If the T score is between –1.0 and 0, the goal of treatment is primary prevention. The recommended calcium and vitamin intake should be achieved and a regular exercise regimen started. If the urine calcium is elevated, small doses of a thiazide diuretic are appropriate. In postmenopausal women, hormone replacement therapy should be considered if no significant risks for estrogen-associated complications are present. In men with evidence of hypogonadism, testosterone therapy should be prescribed.

If the T score is less than –1.0, the same preventive recommendations apply, but calcitriol or a bisphosphonate should be also prescribed.

If secondary hyperparathyroidism is present, calcitriol should be used to improve calcium balance. Monitor the serum (or ionized) calcium at 1-month intervals initially and repeat the urine calcium 1 month after initiating therapy and periodically thereafter. The finding of mild elevations in urine or serum calcium levels should result in reduction in the dose of calcium supplements or the calcitriol or both.

FOLLOW-UP

To determine the effectiveness of these measures, repeat the DEXA 6 months after starting antiosteoporosis therapy in patients who have recently (within 12 months) begun steroid therapy. In patients who have been taking steroids for more than 12 months, repeat DEXA should be performed at intervals of 1 or 2 years. A decrease in bone mineral density of 5% or more warrants either modification of the current intervention or initiation of additional pharmacologic strategies.

Changes in bone architecture

At a histomorphometric level, bone volume is reduced and trabecular thickness declines. As trabecular volume falls below a certain limit, perforations occur, disrupting the three-dimensional trabecular structure.[18] This combination of reduced mass and disrupted architecture dramatically increases the risk of fractures.

RISK DEPENDS ON DOSE AND DURATION OF GLUCOCORTICOID THERAPY

Glucocorticoid-induced bone loss appears to depend on both the dose and the duration of treatment, although there is no established threshold cumulative dose (TABLE 2). Mean doses of prednisone as low as 7.5 mg daily

have been associated with a decrease in bone mass.[19] Moreover, alternate-day therapy has not shown benefit over continuous regimens in reducing rates of bone loss.

In general, inhaled steroids are considered safer than systemic steroids, but they still can cause some bone loss.[20] The daily inhaled dose appears to be the most important determinant, with daily doses less than 1,000 µg considered relatively safe.[21,22]

Age, gender, and race are not risk factors

Age, gender, and race do not appear to be independent risk factors for steroid-induced osteoporosis.[23] Although some studies have suggested that the high rate of bone turnover in children may predispose them to lose bone mass more rapidly than adults, postmenopausal women appear to be at the greatest risk for fractures, possibly due to their added risk imposed by estrogen deficiency.

Individuals vary in their response to steroid treatment. Up to 20% of patients receiving long-term steroid therapy do not develop osteopenia, perhaps because they have some genetically determined lack of susceptibility.

Other risk factors

Cigarette smoking and excessive alcohol consumption should be identified, although it is difficult to quantify their direct contribution in glucocorticoid-induced bone loss.

Inadequate calcium or vitamin D intake may exacerbate the glucocorticoid-induced adverse effects on calcium balance.

The disease being treated by glucocorticoids may also have an effect on bone loss. Limitations in physical activity imposed by the disease may further decrease bone formation, and specific aspects of the pathophysiology of the disease (eg, increased cytokines in rheumatoid arthritis) may increase bone resorption directly. Concomitant medications (eg, other immunosuppressive drugs or loop diuretics) can have independent and potentially additive adverse effects on bone mass reduction.

CLINICAL PRESENTATION DIFFERS FROM POSTMENOPAUSAL OSTEOPOROSIS

The first symptom is typically a nontraumatic vertebral or rib fracture. Whereas the lumbar spine is the area most affected by postmenopausal osteoporosis, patients with steroid-induced osteoporosis tend to lose bone mass from the spine, ribs, distal forearm, and proximal femur.[24,25]

Fractures may result from minimal stress, such as sneezing or lifting a light object, and usually occur at a higher bone mineral density than in patients with postmenopausal osteoporosis. In steroid-treated patients, a decrease in bone mineral density of 1 standard deviation increases the risk of vertebral fracture sixfold; in contrast, in postmenopausal patients, the same decrease in bone mineral density increases the risk only twofold.[26] Persons with a lower bone mineral density at baseline probably have a greater risk of fractures.[27]

Osteoporotic fractures can complicate preexisting medical problems. For example, repeated vertebral and rib fractures result in dorsal

TABLE 2

Risk factors for glucocorticoid-induced osteoporosis

Steroid-related factors
- Dose
- Duration

General osteoporosis risk factors
- Cigarette smoking
- Alcohol consumption
- Sedentary lifestyle
- Underlying disease
- Hypogonadism

Additional factors
- Baseline bone mineral density
- Genetic predisposition

Dietary factors
- Low calcium intake
- Inadequate vitamin D intake

Medications
- Thyroid hormone
- Anticonvulsants
- Immunosuppressive agents (eg, cyclosporine)
- Loop diuretics
- Lithium
- GnRH agonists or antagonists

Factors that have no effect
- Age
- Ethnic group
- Gender

Alternate-day dosing of steroids does not decrease bone loss

kyphosis and distortion of the thorax. These deformities can cause progressive loss of lung volume, leading to a restrictive lung pattern—a potentially devastating outcome for a patient taking steroids for a pulmonary condition.

DIAGNOSTIC WORKUP

Measuring bone mineral density at baseline

The most effective strategy for managing glucocorticoid-induced osteoporosis is to identify people at risk early on, and treat them aggressively. Osteopenia or osteoporosis can be diagnosed by measuring bone mineral density, the best determinant of risk of fractures. Several methods are available to measure bone mineral density at various skeletal sites.[28,29]

Dual energy x-ray absorptiometry (DEXA) is the method of choice. It can measure bone mineral density in the axial skeleton, peripheral skeleton, or total body. It is useful for serial follow-up monitoring; a change in bone mineral density of 5% is generally considered clinically significant. The anteroposterior spine and proximal femur (hip) are the usual sites for analysis. Although DEXA of the lateral spine may be more sensitive in detecting early bone loss since it only measures the vertebral bodies (trabecular bone) and not the spinal processes (cortical bone), it has not been shown to be a better predictor of fractures,[30] and is primarily reserved for investigational studies.

The T score may underestimate risk in steroid recipients

The diagnosis of osteoporosis is based on the T score, which reflects the variance (standard deviation) of a patient's bone mineral density from the mean value for a normal 30-year-old reference population. The World Health Organization defines osteopenia as a T score between 1.0 and 2.5 standard deviations below the mean, whereas osteoporosis reflects a bone mass below 2.5 standard deviations.

However, as mentioned above, for each standard deviation decrease in bone mass the risk of vertebral fractures is two to three times higher in patients with glucocorticoid-induced osteoporosis than in women with postmenopausal osteoporosis. Therefore, the use of the conventional T score of –2.5 to define osteoporosis underestimates the risk of subsequent fractures in glucocorticoid-treated patients.

Quantitative computed tomography measures trabecular bone in the vertebral bodies. It is very sensitive for diagnosing osteopenia, but exposes the patient to more radiation and is less reproducible than DEXA. This limits its clinical utility in patients with glucocorticoid-induced osteoporosis.

Single-photon absorptiometry, single energy x-ray absorptiometry, and radiographic absorptiometry measure bone at appendicular sites only, limiting their usefulness.

Quantitative ultrasonography has the advantages of low cost and no radiation exposure. Ultrasound studies have shown that stiffness of the os calcis in steroid-treated patients is 1 standard deviation below that in age-matched controls.[31] Although recently approved by the Food and Drug Administration, its clinical utility for monitoring response to treatment is still under investigation.

Follow-up bone mineral density studies

In addition to obtaining a baseline assessment to stratify risk, repeat testing after 6 months of glucocorticoid therapy is warranted to give an estimate of the rate of bone loss and the effectiveness of antiosteoporosis therapy. Changes are more likely to be seen at central sites such as the spine than in the appendicular skeleton. If a patient continues to take glucocorticoids longer than 1 year, further follow-up studies every 1 to 2 years are also appropriate.

Biochemical markers of calcium balance

Markers that reflect calcium balance can affect the choice of therapy.

The levels of intact parathyroid hormone and serum calcium can reveal secondary hyperparathyroidism when the PTH level is elevated (> 60 pg/mL) and the calcium level is normal or low. This combination indicates the need for interventions to restore a positive calcium balance (eg, optimizing calcium intake, calcitriol).

A 24-hour urine collection for calcium and creatinine can document hypercalciuria and define the need for a thiazide diuretic to enhance renal calcium reabsorption. A random urinary calcium/creatinine ratio of more than 280 mg/g creatinine (or a 24-hour urinary calcium excretion > 300 mg) is considered sig-

nificant and may warrant intervention.

A free testosterone determination (in men) **and a careful menstrual history** (in premenopausal women) are warranted to assess the impact of glucocorticoids on the gonadal axis.

Biochemical markers of bone turnover are not established

Although assessment of bone turnover is potentially desirable, the clinical utility of measuring markers of bone formation or resorption in steroid-induced bone disease has not been established.

Markers of bone formation. Osteocalcin, a marker of osteoblast function, is suppressed in many patients on steroid therapy.[32–34] However, the finding of low bone formation has no significant effect on choice of treatment, as there are no effective anabolic agents for the treatment of osteoporosis available today.

Markers of bone resorption such as urinary N-telopeptide or pyridinoline or deoxypyridinoline vary greatly in concentration from day to day and do not predict which steroid recipients will develop clinically significant bone disease. The most accepted use of biomarkers of resorption is to assess the response to an antiresorptive regimen early in its course. In postmenopausal osteoporosis, a decrease in bone resorption markers by more than 30% within 3 months of starting treatment has been demonstrated to be related to improvements in bone mineral density after 2 years of treatment. Similar data on using bone resorption markers to predict the response to therapy in steroid-induced osteoporosis are not yet available.

THERAPEUTIC INTERVENTIONS

Ten years ago, few options existed for managing patients with steroid-induced osteoporosis. Today, with new diagnostic techniques more readily available and a new class of drugs (the bisphosphonates), we can hope to reduce the rate of further bone loss and perhaps even prevent osteoporosis (TABLE 3).

Risk factor modifications

Because bone loss increases with the dose and duration of steroid use, it is prudent to use the lowest dose possible for the shortest time. Some of the bone loss may be reversible after steroid withdrawal, at least in the young.[35,36] Therefore, substituting a nonsteroidal agent or discontinuing the steroid as early as possible may improve long-term outcome. When possible, topical or inhaled steroids are preferable to systemic dosing, although bone loss can also occur with these agents if the dose is high enough. Alternate-day dosing may be beneficial for the hypothalamic-pituitary-adrenal axis, but does not significantly decrease the rate of bone loss.

Lifestyle modifications such as stopping smoking, minimizing alcohol consumption, and exercising may reduce bone loss. If the primary medical condition allows, patients should begin a regimen of regular weight-bear-

TABLE 3

Treatment options for glucocorticoid-induced osteoporosis

Risk factor modifications
- Minimize steroid exposure
  - Use lowest dose, shortest duration
  - Use topical steroids when possible
- Minimize medications that can cause additional loss
- Lifestyle modifications
  - Stopping smoking
  - Avoiding excessive alcohol
  - Weight-bearing exercise
- Correct negative calcium balance
  - Elemental calcium 1,500 mg/day
  - Vitamin D 800 IU/day

Pharmacologic interventions
- Calcitriol 0.5–1.0 μg/day
- Bisphosphonates
  - Etidronate 400 mg/day for 14 days every 3 months
  - Alendronate 10 mg/day
- Estrogen replacement therapy
  - (postmenopausal or estrogen-deficient premenopausal women)
- Testosterone
  - (men)

Interventions with unproven benefit
- Calcitonin
- Thiazides
- Fluorides
- Anabolic steroids
- Progesterone
- Selective estrogen receptor modulators
- Intermittent PTH
- Growth hormone and IGF-1

ing or resistance exercise at least 3 days a week for 30 to 60 minutes per day.

Calcium. As steroids create a negative calcium balance, it is important to maintain an adequate calcium intake. Steroid-treated patients should take in at least 1,500 mg of elemental calcium daily. If modifications in the diet cannot meet this level, calcium supplements can be used. Calcium carbonate is the most commonly prescribed form of calcium, owing to its low cost and high percentage of calcium per pill. However, persons with achlorhydria cannot effectively absorb calcium carbonate. Therefore, calcium citrate may be preferred in patients medically treated for gastroesophageal reflux or ulcers or in patients over 70 years of age. Calcium supplements should be given in divided doses (< 600 mg per dose) to enhance absorption.

Vitamin D. It is equally important to take vitamin D to correct any deficiency present. The usual dose of ergocalciferol (vitamin D) is 800 IU/day or 50,000 IU/week. However, neither calcium supplements nor vitamin D prevent steroid-induced osteoporosis by themselves,[37] and most patients need additional agents.

Some bone loss may be reversible after steroid withdrawal

Pharmacologic interventions

Calcitriol is one of the most effective treatments for preventing steroid-induced osteoporosis. At doses of 0.5 to 1.0 μg/day, it can prevent bone loss in the spine but not the femoral neck in patients just started on steroids.[38] With larger doses of steroids, it may not be as effective. Calcitriol therapy is associated with a 25% incidence of mild hypercalcemia, especially in patients taking calcium supplements. Serum calcium and 24-hour urine calcium levels need to be monitored for safety, and doses adjusted accordingly.

Bisphosphonates are pyrophosphate analogues that bind strongly to bone mineral and directly inhibit bone resorption. A cyclic etidronate regimen has been shown to both prevent and treat steroid-induced osteoporosis.[39,40] In addition, recent data have shown that cyclic etidronate therapy can reduce the incidence of new vertebral fractures in postmenopausal women who had recently started high-dose steroids.[41]

Etidronate must be given on an empty stomach, and food and beverages must be avoided for 2 hours before and after each dose. It must be given in a cyclical fashion to avoid a mineralization defect that can occur with prolonged daily use (ie, > 6 months). It is well tolerated with no upper gastrointestinal side effects.

Alendronate (10 mg/day) has also shown beneficial effects on bone turnover[42,43] and bone mineral density[43,44] in patients receiving steroid therapy. Alendronate should be taken first thing in the morning with a full 8-oz glass of water to enhance absorption and reduce its primary side effect of esophageal irritation. Patients should neither eat nor drink anything nor lie down for at least 1/2 hour after taking it.

Estrogen replacement therapy. Menopause may accelerate glucocorticoid-induced osteoporosis. The limited data that exist on the use of estrogen in managing steroid-induced osteoporosis indicate that it may increase bone mineral density slightly in the lumbar spine but may not prevent bone loss in the femoral neck.[45,46] Other estrogen benefits include improvement in lipid status, reduction in cardiovascular disease risk, and perhaps a reduction in the risk for developing memory loss or Alzheimer disease. These benefits come at an added risk for breast cancer with long-term use and venous thromboembolic disease in susceptible individuals. The risk-benefit ratio may, however, favor hormone replacement, at least in the short term.

The usual dose of estrogen is 0.625 mg/day of conjugated equine estrogens or 1 mg/day of estradiol. Progesterone, in either a continuous or cyclical regimen, should be added if the uterus is still intact to prevent endometrial hyperplasia or cancer.

Testosterone replacement should be offered to men with hypogonadism. This therapy can reverse some of the negative effects on body composition that steroids cause, and may produce small increases in bone mineral density in the lumbar spine but not the hip.[47] Depo-Testosterone (200 mg intramuscularly every 2 weeks) or one of the transdermal testosterone preparations can be used. Long-term use of oral testosterone should be avoided due to the potential, although uncommon, risk of hepatic tumors.

Interventions with unproven benefit

Calcitonin. Data conflict regarding the efficacy of calcitonin.[38,48–52] Early studies with injectable calcitonin showed some benefit in preventing bone loss, especially in the first year of steroid use.[48,49] However, more recent studies have shown no significant benefit over placebo,[38,50] and there are no data to support a favorable effect on reducing fracture rates. Its primary clinical utility has been in patients with osteoporotic vertebral fractures and increased pain. The usual dosage is 200 units daily intranasally (in alternating nostrils), or 100 units every day or every other day subcutaneously or intramuscularly.

Thiazide diuretics. There are limited data on the use of thiazide diuretics in involutional osteoporosis, and no data at all supporting their use in steroid-related bone loss. In theory, since steroids induce a renal calcium leak in some patients, a thiazide would help to minimize calciuria. In a patient with a urine calcium level greater than 300 mg/day (or > 4 mg/kg/day), a thiazide would be appropriate in concert with other preventive or treatment strategies. Short-term use may be less beneficial than long-term use.[53] Serum and urine calcium and serum potassium levels should be monitored for safety and efficacy.

Fluoride directly stimulates bone formation by enhancing the recruitment and differentiation of osteoblasts. In studies in postmenopausal osteoporosis, sodium fluoride produced significant gains in bone mineral density at both the spine and hip, but also an increased rate of fractures in the appendicular skeleton. In steroid-treated patients, when sodium fluoride is given in combination with etidronate, there is an apparent additional increase in bone mineral density.[54] However, there are no data regarding its effect on fractures in steroid-treated patients.

Recent trials have focused on a new, well-tolerated, extended-release form of sodium fluoride, sodium monofluorophosphate. The use of this agent (200 mg/day) has been associated with increases in lumbar spine bone mineral density in patients on steroids.[55,56] Further studies are needed before those agents can be routinely recommended for clinical use.

Other agents proposed for managing steroid-induced osteoporosis include anabolic steroids and progestational agents. **Nandrolone decanoate** inhibits bone resorption as manifested by decreased urinary excretion of hydroxyproline[57,58] and increased bone mineral density in the forearm. **Medroxyprogesterone acetate** has been shown to improve bone density in men taking glucocorticoids long-term.[59,60] Its mechanism of action is postulated to be through enhanced osteoblastic activity as suggested by increases in serum osteocalcin levels with treatment. New medications under investigation include the selective estrogen receptor modulators such as **raloxifene**, and anabolic regimens such as intermittent **PTH**, and **growth hormone and IGF-1**.

Calcitriol prevents bone loss in the spine

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