Drug-induced osteoporosis

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■ Use of corticosteroids has been most frequently associated with bone loss, but heparin and methotrexate, when used in relatively high doses, have also been linked to the development of osteoporosis. Clinical features of bone loss associated with these agents, possible pathophysiologic mechanisms, and strategies for avoiding this complication are reviewed.
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IDENTIFICATION of so-called secondary causes of osteoporosis is an important part of the evaluation of patients with osteopenia. While corticosteroids have long been recognized as the class of drugs most commonly implicated in bone loss, relatively high doses of heparin and methotrexate have also been associated with development of osteoporosis. This potential complication is of great interest, especially since methotrexate is now being widely used in low-dose pulse fashion to treat rheumatoid, as well as psoriatic, arthritis. This review focuses on heparin, methotrexate, and corticosteroids as agents with potential for inducing bone loss.

HEPARIN

High-dose (10,000–20,000 U daily) chronic heparin therapy is employed infrequently in selected clinical situations. Recurring thromboembolic disease, particularly during pregnancy, is probably the most common clinical situation in which this form of therapy is considered. Levine[1] believed ischemic heart disease and peripheral arterial disease were clinical indications as well.

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The association of high-dose chronic heparin therapy with the development of osteoporosis was first reported in 1965.[2] Fewer than 50 cases have been noted in the medical literature since then, and the true incidence of this complication is unknown. Griffith et al[2] reported studies of 117 patients on long-term heparin therapy and compared the frequency of osteoporotic fractures in patients receiving less than 10,000 U daily for as long as 15 years with the frequency in patients taking 15,000–30,000 U daily for six months or longer. No patients on low-dose therapy showed signs or symptoms of osteoporotic fracture, whereas six of the 10 patients on the higher dose had spontaneous vertebral or rib fracture. Later investigations[3–6] similarly found cases of osteopenia in patients treated with high-dose heparin for a variety of indications. Rupp et al[4] reported that osteoporosis, defined by plain radiographs showing evidence of demineralization and/or compression fracture, developed in six of 25 patients treated with continuous intravenous heparin at a mean dose of 21,000 U daily.

The only prospective study of high-dose chronic heparin therapy in pregnant women was reported by Howell et al in 1983.[3] Forty patients were randomly assigned to receive either 20,000 U of heparin daily or no treatment. "Severe debilitating osteopenia" developed in one of the 20 heparin-treated patients. Obviously, the numbers in the study groups are too small to demonstrate significant difference in risk.

In all the above reports, the minimum daily dose of heparin was 15,000 U or more, except in one case in which the daily dose was 10,000 U. All patients were treated for more than six months. No other risk factors for osteoporosis were reported in most patients. Back pain was usually the presenting symptom. Rapid abatement of pain following discontinuation of heparin had been reported by several patients.[7] Histologic evaluation of bone in heparin-induced osteoporosis by nondecalcified bone biopsy was reported by Zimran et al.[8] Transiliac bone biopsy was performed 18 days following discontinuation of heparin therapy in a 23-year-old woman with compression fractures of T-12 and L-1 who had been treated for seven months while pregnant with 15,000 U of heparin daily. Though there was a slight decrease in trabecular bone volume, the striking finding was a substantial increase in osteoid surface with little evidence of resorptive activity. The mineralization rate was normal. This was interpreted as suggesting some recovery from the osteoporotic state.

Pathogenesis

The mechanism of heparin-associated osteoporosis is not well defined. Avioli[9] reviewed the studies of heparin and heparin-related substances in animals and their effects on bone. He suggested several potential mechanisms, including:

1. Direct effect of heparin on bone cells with a net decrease in osteoblastic activity and some evidence for increased osteoclastic activity;
2. Interference with utilization of the normal matrix mucopolysaccharides of bone, resulting in defective ossification;
3. Decrease in ionized calcium and resultant secondary hyperparathyroidism and bone loss; and
4. Effect of a heparin-related increase in mast cells on bone.

Which, if any, of these potential mechanisms is of importance is unknown. Aarskog et al[10] suggested an effect of heparin on vitamin D metabolism as a further potential explanation for the bone loss seen in these patients.

Treatment

Presently, discontinuation of heparin is the only treatment for this complication of therapy.[11]

METHOTREXATE

Methotrexate is a folic acid analogue whose principal mechanism of action is the competitive inhibition of the enzyme folic acid reductase.[12] As the conversion of dihydrofolate to tetrahydrofolate is inhibited, tissue-cell reproduction is impaired.

Methotrexate has been used in the treatment of childhood lymphocytic leukemia for over four decades.[13] It has been very effective in the treatment of choriocarcinoma in women. Along with its usefulness in lymphomas and osteogenic sarcoma, methotrexate has been beneficial in patients with carcinoma of the bladder, breast, and pharynx.[14] Since the early 1950s, methotrexate has been used to treat severe cases of psoriasis.[15] More recently, methotrexate has been shown to be beneficial in the treatment of rheumatoid arthritis;[16–18] its use in rheumatoid arthritis has now been approved by the FDA. In addition, there are several reports of methotrexate being used to treat polymyositis, Wegener's granulomatosis, systemic lupus erythematosus, and polyarteritis nodosa.[17–24]

In the treatment of childhood leukemias, it is often necessary to maintain relatively high doses of oral methotrexate for extended periods. Several authors have suggested that chronic high-dose methotrexate used to treat childhood acute leukemia is associated with osteoporosis.[25–28] Ragab et al[27] reported that the osteoporosis was associated with bone pain and fractures in children on oral methotrexate for maintenance chemotherapy. This group noticed marked improvement in bone pain and resolution of osteoporosis in four out of five children within four months of cessation of methotrexate therapy. Nesbit et al[26] observed bone pain, osteoporosis, and fractures in 26 of 216 children with acute lymphocytic leukemia. Stanisavljevic and Babcock[28] reported osteopenia in 20 of 37 children treated with methotrexate for acute leukemia, seven of whom sustained multiple fractures.

Findings from animal studies addressing methotrexate-induced metabolic bone disease have been scant. In one controlled study, Friedlaender et al[29] administered high-dose methotrexate to rats for five days. They reported a 25% reduction in net trabecular bone of tail vertebrae nine days after cessation of the drug. Bone formation rates decreased by 60% in the experimental group. Although the total number of osteoblasts was not different at 14 days in the two groups, osteoid thickness was reduced in patients treated with methotrexate, suggesting an inhibition of osteoblastic function by the drug.

Pathogenesis

The pathogenesis of methotrexate-induced osteopathy is unknown, and available evidence is conflicting. It has been observed that children on methotrexate for prolonged periods grow normally.[30,31] Nevinny et al[32] observed a moderate increase in urinary and fecal calcium excretion in eight patients with neoplastic disease being treated with methotrexate. Collectively, these findings tend to suggest that methotrexate-induced osteopenia is caused by an increase in resorption of calcium from bone rather than a primary problem of decreased bone formation, as suggested by the rat studies of Friedlaender et al.[29]

Further studies are necessary to define more clearly the mechanism of methotrexate-induced osteoporosis. No data are available on the influence, if any, of low-dose methotrexate on bone physiology. As long-term, low-dose methotrexate is used more frequently for such diseases as rheumatoid arthritis and psoriasis, findings on the effects of low-dose methotrexate on calcium and bone metabolism are awaited.

CORTICOSTEROIDS

While the association of corticosteroid therapy with osteoporosis in rheumatic and other diseases is recognized, many unanswered questions about the relationship remain. The association of osteoporosis with exogenous corticosteroid therapy in both pulmonary and rheumatic disease was first recognized more than 30 years ago and is widely accepted today. Approximately 80%–90% of Cushing's syndrome patients have significant osteopenia, as determined by radiologic and histologic criteria.[33]

The relationship between chronic corticosteroid therapy and osteoporosis in rheumatic and pulmonary diseases is difficult to define. A major reason is that confounding factors predispose an individual to osteopenia and are difficult to quantify accurately or separate from the effect of corticosteroid therapy itself on bone.

For example, reduced physical activity might be a potential risk factor for the development of osteoporosis in many patients with chronic lung and arthritic disorders. This variable is difficult to quantify. Furthermore, it is usually the sicker patient (i.e., also less active) who becomes a candidate for corticosteroid therapy.

Rheumatic disease

Early investigators, using plain spine radiographs as the predominant tool for identifying osteoporosis, found little evidence that corticosteroid therapy increased the risk of osteoporosis in patients with rheumatoid disease.[34,35] More recent investigators employing forearm densitometry[36] and total-body calcium measurement[37] have more clearly demonstrated excessive bone loss in steroid-treated patients with rheumatic disease, as compared to nonsteroid-treated controls.

Other investigators have evaluated patients with rheumatoid diseases and osteoporosis from the standpoint of risk factors for bone loss.[38–42] Results from these studies of the role of corticosteroids as an independent risk factor are conflicting. Hooyman et al[39] identified increased risk of osteoporotic fracture associated with increasing age, earlier age at diagnosis of rheumatoid arthritis, disability, impaired ambulation, steroid use, and thinness. However, in multivariate analysis, only aging, impaired ambulation, and thinness were identified as independent risk factors. Dykman et al,[40] using forearm densitometry in 161 ambulatory patients receiving long-term corticosteroid therapy for rheumatic disease, found large cumulative doses of prednisone were associated with fracture, as well as bone loss. They noted that cumulative dose, rather than daily dose, was important in predicting osteoporosis risk. Kennedy et al,[38] evaluating femoral shaft bone mass by caliper measurement, found no difference between steroid-treated and nonsteroid-treated patients. Similarly, Sambrook et al[41] used dual-photon spinal and femoral neck densitometry to assess bone loss in 111 patients with rheumatoid arthritis. The most significant correlate of bone-mineral density was physical activity. Prednisolone (mean dose, 8 mg per day) was not associated with significantly increased bone loss in women.

Pulmonary disease

Chronic steroid therapy in pulmonary diseases has been less extensively studied in terms of bone loss. Mueller[42] reported results of forearm bone-density measurements in 114 asthmatic patients, some of whom had been treated with corticosteroids. No relationship between corticosteroid dose and bone mineral density was found. Adinoff and Hollister[43] reported a similar study in 128 corticosteroid-treated asthmatic patients compared with 54 asthmatics who had not received long-term corticosteroid therapy. Trabecular bone mass was decreased in the corticosteroid-treated patients, but no significant correlation between bone density and duration of steroid treatment was noted.

Dosage

As discussed previously, some investigators have noted a relationship between daily dose of corticosteroid and risk of osteopenia.[37,40] Dykman's group noted that, even at doses of prednisone equivalent as low as 5 mg daily, long-term treatment was associated with increased risk of osteopenia and fracture. Cumulative dose, therefore, may be more critical than daily dose in determining risk of osteopenia.

Early studies of young rabbits suggested that alternate-day administration of corticosteroids lessened effects on bone.[44] However, Gluck et al[45] reported no significant difference in bone density, as determined by forearm densitometry in daily steroid-treated patients, compared to patients treated with alternate-day glucocorticoids.

Pattern of bone loss

The osteoporosis of glucocorticoid therapy may be associated with greater loss of trabecular bone than cortical bone.[33] In forearm densitometry studies, this is reflected by an increase in diaphyseal to metaphyseal mass ratio (DM:MM). This finding reflects the fact that the metaphyseal measurement site contains a higher proportion of trabecular bone than the diaphyseal site. Hahn[33] observed that this pattern is similar to the pattern noted in patients with osteopenia as a result of primary hyperparathyroidism. Results of nondecalcified bone biopsy studies of patients taking corticosteroids chronically have revealed a marked reduction of trabecular bone volume, as well as increased trabecular resorptive surface area.[46] A marked decrease in osteoblastic appositional rate has also been observed. These findings suggest that the lesion in corticosteroid osteoporosis reflects increased osteoclast activity (resorption), as well as decreased osteoblast activity (formation). The net result is, obviously, decreased bone mass.

Pathogenesis

The pathogenesis of corticosteroid osteoporosis is controversial, but may include several elements:

1. Direct effect of glucocorticoids on osteoblasts and osteoclasts.
2. Impaired calcium absorption and resultant secondary hyperparathyroidism.
3. Hypercalciuria and resultant secondary hyperparathyroidism.

Studies of enriched cell populations of osteoblasts and osteoclasts in tissue culture have revealed the presence of corticosteroid receptors in both cell populations. Chen and Feldman[47] observed that dexamethasone inhibited cell growth of both osteoblasts and osteoclasts in vitro, and that parathyroid hormone had an enhanced effect on dexamethasone-treated osteoblasts. Weisman et al[48] reported further evidence of a direct corticosteroid effect on osteoblasts. They measured bone gammacarboxyglutamic acid-containing protein (BGP) in patients with rheumatoid arthritis. BGP is the chief noncollagenous protein of bone and a plasma marker for bone formation. Steroid treatment was a major determinate of low BGP levels; women taking steroids had the lowest levels.

Corticosteroid therapy results in reduced intestinal calcium absorption.[49,50] The mechanism of corticosteroid-related calcium malabsorption is not well understood. Klein et al[50] reported decreased levels of 25-hydroxyvitamin D in steroid-treated patients, but this finding was not substantiated by Slovik et al,[51] who did not find significant abnormalities of vitamin D metabolism in glucocorticoid-treated patients.[50,51] While calcium malabsorption clearly occurs, secondary hyperparathyroidism is less well documented. As noted previously, forearm densitometry in glucocorticoid-treated patients resembles that of the hyperparathyroid state,[33] but studies measuring parathyroid hormone levels in glucocorticoid-treated patients are conflicting.[51–53]

Hypercalciuria in steroid-treated patients is well recognized.[54,55] The same studies have reported elevated parathyroid hormone levels in steroid-treated hypercalciuric patients, as well as increased nephrogenous cyclic adenosine monophosphate levels. Based on this work, it has been proposed that hypercalciuria from corticosteroid therapy results in secondary hyperparathyroidism and eventual osteopenia. This concept suggests a potential role for thiazide diuretics as antagonists of urinary calcium excretion in the management of corticosteroid osteopenia.[54,55]

Minimizing effects of corticosteroids on bone

Despite well-known and well-defined toxicity, corticosteroids play a major role in the management of a range of immunologic, pulmonary, and rheumatic disorders. Clinicians have long been interested in ways of minimizing the effect of corticosteroids on bone. Based on the above discussion of pathogenesis, several possible approaches are apparent:

1. Discontinue corticosteroid therapy.
2. Minimize exposure to corticosteroid therapy by using the lowest possible daily dose for the shortest possible time.
3. Alternate-day corticosteroid therapy.
4. Improve calcium absorption by vitamin D and/or calcium therapy.
5. Block steroid-induced hypercalciuria with thiazide diuretics.
6. Develop corticosteroid agents with less effect on bone than those presently available.
7. Use an agent known to stimulate osteoblastic ac-

tivity (i.e., sodium fluoride).

Discontinuation of corticosteroids has been shown to be followed by a rebound increase in osteoblastic function.[56] Unfortunately, in many patients with rheumatic, pulmonary, or allergic disorders, discontinuation of steroid therapy is not feasible. Based on the recent observations of Dykman et al,[40] who associated greatest risk of osteoporosis with increasing cumulative dose, using the lowest possible dose of corticosteroid for the shortest possible time should offer some help in reducing the impact of corticosteroid on bone. Whether there exists a "safe" threshold–a daily corticosteroid dose below which there is minimal effect on bone–is an unresolved question.[41]

Although alternate-day therapy initially appeared to be an attractive option, studies suggest alternate-day therapy is not protective of bone loss.[45]

It is tempting to postulate that calcium malabsorption induced by steroids might respond to calcium and/or vitamin D therapy. Hahn et al[53] reported the effectiveness of a regimen of 500 mg of calcium and 40 µg of 25 hydroxyvitamin D daily in the management of patients with rheumatic diseases receiving a mean dose of 17.5 mg of prednisone daily. This group showed marked improvement in calcium absorption and reduction of elevated parathyroid hormone levels. Radial forearm densitometry revealed an increase in metaphyseal bone mass of approximately 13% within one year of therapy. A more discouraging report by Rickers et al[57] compared triple therapy with calcium fluoride and vitamin D with no therapy in 31 patients receiving 20–25 mg of prednisone for 24 weeks. No significant difference in forearm bone density measurements was noted. Dykman et al[58] reported a trial of oral calcium and 1,25 dihydroxyvitamin D in a group of patients with rheumatic disease and glucocorticoid-induced osteopenia. No significant gain in forearm bone mass occurred and fractures were frequent in both treated patients and those receiving a placebo. Concern has been raised about hypervitaminosis D and resultant hypercalciuria or frank hypercalcemia in patients with glucocorticoid osteoporosis treated in the above fashion.[59]

Preliminary studies in a small number of cases suggest that hydrochlorothiazide twice daily may decrease calcium excretion in steroid-treated patients.[54,55] Effect on bone density and, more importantly, fracture risk has yet to be clarified.

Deflazacort, a prednisolone derivative, is being studied as a bone-sparing corticosteroid. Earlier reports described significantly less hypercalciuria in deflazacort-treated patients as compared to prednisone-treated patients.[60,61] Whether this represents any clinically significant advantage is unclear. Interestingly, deflazacort appears to have less impact on glucose metabolism[62] and differing effects on leukocyte subpopulations,[63,64] compared with prednisone.

The use of agents or factors known to stimulate osteoblastic activity such as sodium fluoride, growth hormone, or other "growth factors" (skeletal growth factor, bone derived growth factor, macrophage derived growth factor) has not been extensively studied clinically in the management of corticosteroid osteoporosis.

Recommendations

Based on currently available information, it seems reasonable to recommend for patients undergoing long-term corticosteroid therapy:

1. Adequate calcium supplementation.
2. Adequate vitamin D (400 U daily in patients without significant sun exposure). In patients with suboptimal 24-hour urinary calcium levels despite calcium supplementation, vitamin D supplementation may be considered. On such a regimen, monitoring 24-hour urinary calcium levels for significant hypercalciuria may be necessary.
3. Minimizing the dose and duration of corticosteroid therapy.
4. In high-risk patients (postmenopausal, the elderly, those on higher-dose corticosteroid, and those with impaired ambulation), investigational therapy using, for example, sodium fluoride or hydrochlorothiazide, may be considered.

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