Review Article

OSTEOPOROSIS

Invited Paper

N. Sema Akalın

M.D. Sub-department of Endocrinology, Department of Internal Medicine, School of Medicine, Marmara University, Istanbul Turkey.

ABSTRACT

Osteoporosis represents the most common form of metabolic bone disease. Its epidemiology, pathogenesis, clinical manifestations, radiographic and laboratory features, bone density measurements, and treatment are discussed.

Key Words : Postmenopausal osteoporosis, Bone mineral density, HRT, Bisphosphonates

INTRODUCTION

Osteoporosis is the most commonly encountered bone disease. It is a major risk factor for fracture and leads to considerable morbidity, mortality and expense. This skeletal disorder is characterized by two elements that distinguish it from other causes of osteopenia such as osteomalacia and hyperparathyroidism : low bone mass and microarchitectural disruption.

Low bone mass is a characteristic finding in osteoporosis. The bone that is present is normally mineralized, which distinguishes osteoporosis from osteomalacia (1).There is disruption of the normal architecture.Fewer bony spicules are seen in osteoporotic bone and they are thinner than normal ; in addition,there are horizontal "struts" that do not join up to any other structure, and thereby provide no structural support. This microarchitectural disruption leads to skeletal fragility (2,3).

This strict definition of osteoporosis is largely histologic. In practice, one deals mainly with decreased bone density, or osteopenia, without examining bone histology. Osteopenia (thin bones) is due in large part to osteoporosis as defined above, although there are other contributors such as mild vitamin D deficiency or hyperthyroidism.

EPIDEMIOLOGY

It is estimated that over 1.3 million osteoporotic fractures occur each year in the United States. Approximately one-half of these fractures are vertebral fractures, one-quarter are hip fractures, and one-quarter are Colles' fractures (2). Pelvic and hip fractures are associated with increased mortality, although conditions other than the fracture itself may account for most of the deaths (4).The risk of all fractures rises dramatically with age but osteoporotic fractures are not limited to the elderly.

The number of women at risk for fracture because of radiographic osteoporosis (defined as bone mineral density more than 2 SD below the mean of young women) is much higher than the number of women who actually have fractures.Approximately 30 percent of women over the age of 50 have low bone mass, and the numbers increase with age.Low lumbar spine bone mineral density is present in 15 percent of women in the sixth decade, and in nearly one-half of all women in the eighth and ninth decades.When a more strict definition of osteoporosis (2.5 SD below the mean of young women) is used, the prevalence is 13 to 18 percent in women above age 50 years, and 3 to 6 percent in men above age 50 years (5).

The burden of osteoporosis is borne disproportionally by women. After age 50, a woman is three times more likely than a man to have a vertebral or hip fracture (16 to 18 versus 5 to 6 %) and six times more likely to have a Colles' fracture (6). It has been estimated that as much as 75 percent of bone lost in the years after menopause may be related to estrogen deficiency rather than age (7).

PATHOGENESIS

Osteoporosis is the end result of years of bone loss, which is always due to a mismatch between bone resorption and bone formation. Both bone resorption and formation are increased in postmenopausal

(Received 3 June, 1999)

women (8,9), hyperparathyroidism (10), hyperthyroidism (11), and malnutrition. However, resorption outpaces formation in these disorders, resulting in high-turnover osteoporosis. Patients with anorexia nervosa, for example, tend to have low bone density, which is more than two standard deviations below normal in 50 % (12). The bone loss is caused by low production of both estrogen (13) and insulin-like growth factor-1 (14,15). Exercise appears to minimize the bone loss in these patients and bone density improves with recovery and resumption of normal menses (13). The mechanism by which estrogen lack leads to increased bone loss is not well understood. Both direct effects on osteoclast function and changes in the release of certain cytokines appear to contribute. Bone resorption and formation are reduced in patients with liver disease; however, formation is impaired to a greater extent than resorption, resulting in low-turnover osteoporosis (16). Bone resorption is accelerated and formation is slowed by excess glucocorticoids. This combination can lead to extremely rapid bone loss. Certain drugs such as heparin, cyclosporin, medroxyprogesterone acetate, vitamin A, certain synthetic retinoids and perhaps warfarin, can also cause bone loss. Most patients with osteoporosis, however, do not have any of these primary diseases, and their bone loss is largely due to two factors: age-related bone loss and menopause-related bone loss.

Age-related bone loss – Age-related bone loss begins in the fourth or fifth decades, and results in a slow loss of cortical and trabecular bone in both men and women (17). This loss may be partially due to decreased calcium absorption, and may be somewhat attenuated by calcium supplementation (18).

Menopause-related bone loss – Menopause related bone loss begins soon after the onset of estrogen deficiency. A rapid acceleration of bone loss is particularly seen in trabecular bone (17). After the menopause, the ovaries in many women continue to secrete a small amount of estradiol, while in others there is no estradiol secretion. When these two groups were compared about twenty years after the menopause, those with undetectable concentrations of serum estradiol had more bone loss (19) and a relative risk of vertebral and hip fracture of 2.5 compared to women who had measurable serum estradiol (20). Estrogen replacement therapy, progestins and bisphosphonates can attenuate this loss (8,21-23). Menopause-related bone loss lasts for about 10 years. After this time, the rate of bone loss is diminished to near the rate of aging (17).

Osteoporosis in men – Gonadal failure and androgen insensitivity are also risk factors for osteoporosis in men (24-26). All men with otherwise unexplained osteoporosis should be asked about symptoms of hypogonadism (decreased libido, impotence and testicular atrophy) and the serum testosterone concentration should be measured. In addition to testosterone, estrogen has an important effect upon bone metabolism in men. In one study, bone density at all skeletal sites in men over the age of 65 was positively correlated with higher serum estradiol concentrations, even after adjustments for weight and serum sex-hormone binding globulin concentrations (27). Low bone density has also been described in patients with marked estrogen deficiency due to a defect in the estrogen receptor gene, and estrogen deficiency due to a loss-of-function mutation in the aromatase gene (28,29). Similarly, studies in postmenopausal women suggest that low serum androgen concentrations may contribute to the bone loss associated with estrogen deficiency (30).

Genetic factors – Genetic factors most likely play a contributory role in bone density status. Among the genes that have been studied is the vitamin D receptor gene. Allelic variation in this gene could theoretically affect the ability to bind vitamin D (directly or due to variation in the number of receptors), thereby predisposing some patients to reduced bone mineral density and later,osteoporosis (31). Another gene that has been associated with bone density is COLIA1, the gene for collagen type Ialpha1, a bone matrix protein. COLIA1 polymorphism has been detected in 1700 postmenapausal women with reduced bone density (32).

An increased fracture risk may also be due to previous fractures, cigarette smoking, malabsorptive gastrointestinal diseases including cystic fibrosis, previous hyperthyroidism, sedentary life style, low body weight or weight loss, and anxiolytic, anticonvulsant, or neuroleptic drugs (33-36).

TYPES OF OSTEOPOROSIS

The bimodal nature of postmenapausal bone loss warrants a distinction between two different syndromes: type I and type II osteoporosis. Type I osteoporosis is due to rapid trabecular bone loss after menapause. Its primary clinical manifestations are distal forearm and painful vertebral compression fractures 10 to 20 years after menapause. Slow cumulative loss of both cortical and trabecular bone causes type II osteoporosis. Its primary manifestations are hip fractures and painless vertebral wedge fractures at the ages of 70 to 90. The vertebral wedge fractures are painless because bone loss is slow and the fractures are gradual. Many patients may be hard to classify.

CLINICAL MANIFESTATIONS

Osteoporosis has no clinical manifestations until there is a fracture. In comparison, pain is common in osteomalacia. Vertebral fracture is the most common clinical manifestation of osteoporosis. About two-thirds of these fractures are asymptomatic and they are diagnosed as an incidental finding on chest x-ray. Osteoporotic fracture can lead to the acute onset of pain, typically occuring during routine activities, such as bending and pulling. The acute pain diminishes in several weeks and is replaced by a chronic dull pain which can persist for a prolonged time in some patients. Successive crush fractures can cause thoracic (dorsal) kyphosis with height loss and the dowager's hump (3). Patients note that they no longer have a waist. They may complain of muscular neck pain, since they have to extend their necks in order to look forward. Multiple vertebral compression fractures lead to discomfort in the hips, especially in the area of the superior iliac crest. This symptom is due to a reduction in the normal distance between the bottom of the rib cage and the top of the iliac crests; the rib cage may bounce on the iliac crests causing pain. Dyspnea and gastrointestinal complaints (early satiety,constipation) may arise.

Hip fractures are relatively common in osteoporosis, affecting 15 % of women and 5 % of men by 80 years of age. Distal radius fractures (Colles) may also occur (37).

RADIOGRAPHIC FEATURES

Plain radiographs show detectable changes when bone loss exceeds 30 percent. The vertebral bodies may appear as empty shells. Thinning and loss of trabecular pattern also occurs in the femoral neck.

In the spine, an early manifestation is "codfishing" ; this occurs when the intervertebral disc causes a central depression in the middle of the vertebral body. Spinal osteoporosis can also lead to compression fractures or wedge fractures. Anterior wedging is usual and posterior wedging is uncommon. Wedge fractures may cause forward-thrusting thoracic kyphosis. Thoracic kyphosis can also result from misalignment of perfectly rectangular, nonosteoporotic vertebral bodies. This important distinction is made by lateral spine or chest x-ray (17).

LABORATORY STUDIES

Evaluation should include a chemistry profile, complete blood count, and serum thyrotropin (TSH) measurement. Normal serum bicarbonate, calcium, TSH and creatinine values exclude potentially treatable conditions such as metabolic acidosis, hyperparathyroidism, hyperthyroidism and renal insufficiency. Normal serum calcium, phosphate, albumin and alkaline phosphatase values mitigate against osteomalacia, while a normal blood count and calcium concentration makes myeloma unlikely. The serum alkaline phosphatase concentration may be high in patients with recent healing fractures. Thus, an isolated high value in a patient with a recent fracture is of limited significance.

The serum testosterone concentration should be measured in men with osteoporosis, particularly if there is diminished libido, impotance, or testicular atrophy (38).

The serum concentration of 25-hydroxyvitamin D and parathyroid hormone (PTH) should be measured if the patient is elderly with poor vitamin D intake or if there is a history of gastrointestinal disease (such as malabsorption or gastrectomy), liver disease, or anticonvulsant therapy. Vitamin D deficiency is associated with low serum 25-hydroxyvitamin D and high serum PTH concentrations due to secondary hyperparathyroidism.

Urinary cortisol excretion or an overnight dexamethasone suppression test should be performed if Cushing's syndrome is suspected.

The serum PTH concentration should be measured in the presence of hypercalcemia or hypercalciuria. A serum and urine protein electrophoresis must be obtained if multiple myeloma is being considered (37).

MEASUREMENT OF BONE DENSITY

The World Health Organization has defined normal bone density as a value within one standard deviation of the young adult mean. Bone mineral density (BMD) in any adult that is between 1 and 2.5 standard deviations below the mean is defined as osteopenia, and values more than 2.5 standard deviations below the mean is defined as osteoporosis and is associated with skeletal fragility; this level is considered to represent the fracture threshold. The lower the bone mass, the greater is the tendency to fracture (2).

There are several different methods used to assess bone density: single and dual photon absorptiometry, dual x-ray absorptiometry, quantitative computed tomography, ultrasonography and radiographic absorptiometry are such methods. Dual x-ray absorptiometry (DXA) gives an accurate and precise estimate of BMD, and is therefore the method of choice (39).

Bone densitometry is indicated whenever a determination of bone density will help guide the therapeutic decision-making process. This can occur in several settings :

*It can be performed around the time of menopause to help guide a decision about estrogen replacement therapy.

*Patients taking long-term glucocorticoid therapy should have baseline and serial measurements of bone densitometry to help guide therapeutic options.

*Patients with asymptomatic primary hyperparathyroidism who might be managed medically should have initial and serial measurements.

MEDICAL THERAPY

Oral calcium supplements, hormone replacement therapy, selective estrogen receptor modulators (SERMs), calcitonin, calcitriol, bisphosphonates and sodium fluoride have all been used in the treatment of osteoporosis.

Calcium Supplements – The effect of calcium supplementation on bone mass and vertebral fracture rate in established osteoporotic states is not well studied. Some studies suggest that calcium supplementation in perimenopausal females does decrease the rate of bone loss when given in doses of 1000-1500 mg/day, especially in subjects with low calcium intakes (40). A combination of calcium supplements and exercise has also proven effective in reducing skeletal bone loss rates in postmenopausal female populations.

Hormone replacement therapy – Estrogen is an "antiresorptive" agent which inhibits bone resorption by decreasing the frequency of activation of the bone remodeling cycle. In the early stages of menopause, when bone turnover is increased, it is expected to be most efficient. The usual starting dose is 0.625 mg of conjugated equine estrogen or 0.05 mg of transdermal estrogen, and they may be given in combination with progesterone. Unwanted symptoms (breast tenderness,spotting,pelvic discomfort and mood changes) related to HRT have limited the number of persons who experience its bone-sparing effects (41).

Selective Estrogen Receptor Modulators (SERMs) These compounds interact with the estrogen receptor but have tissue-specific activities. For example, raloxifene, which is a member of this family, acts as an estrogen antagonist on the uterus and breast but displays estrogen-agonistic activities on bone mass and lipids. This class of drugs may include 1) various agents previously known as antiestrogens, such as 16-epiestriol, ethamoxytriphetol, clomiphene, and tamoxifen ; 2) a 19-nortestosterone derivative, tibolone; 3) raloxifene and its analogs, such as LY 117018 ; and 4) newer triphenylethylene derivatives, such as droloxifene, toremifene, idoxifene, and levormeloxifene. Various doses of raloxifene and elemental calcium have decreased bone turnover markers and significantly increased bone mineral density (42).

Calcitonin – Like estrogen, calcitonin inhibits bone resorption and slows down the rate of bone loss. In patients with increased bone turnover, the response is better than patients with low turnover. The recommended dose is 100 U subcutaneously daily. Intermittent pulse-dose regimens have also been used with documentation of increased bone mass and decreased fracture incidence. Calcitonin has inherent analgesic properties and can be recommended in the early postfracture period because of this effect. Side effects (flushing, nausea) and the development of antibodies may limit its use (43).

Calcitriol – Calcitriol, in a dose of 0.25 (g/day, has been shown to reduce the vertebral fracture rate compared with a group of patients taking calcium alone. In some instances, increments in bone mass of 1-2 %/annum have been recorded. It has also been used in the treatment of steroid-induced osteoporosis. Because calcitriol is the most potent metabolite of vitamin D, it does increase intestinal calcium absorption, often resulting in hypercalciuria and/or hypercalcemia. Patients should be monitored every 6-8 weeks for development of these biochemical abnormalities (44).

Bisphosphonates – This group of compounds includes etidronate, alendronate, pamidronate, tiludronate, risedronate and ibandronate. Efficacy of etidronate (400 mg/day, for two weeks every 3 months, with supplemental calcium) has been demonstrated in postmenopausal women and patients with glucocorticoid-induced osteoporosis. Cyclic etidronate has also been used in combination with estrogen for both prevention and treatment of osteoporosis (45). The long-term efficacy of alendronate (10 mg/day) has been documented in postmenopausal osteoporosis. A meta-analysis has shown a reduction in vertebral and nonvertebral fracture incidence (46). Alendronate is usually well tolerated, but esophagitis and esophageal ulcers can occur.

Sodium fluoride – This compound is used in doses between 50-75 mg/day for the treatment of postmenopausal osteoporosis. Although the increase in spinal bone mass approximates 8%/year, there is little evidence that this increase translates to a

reduction in vertebral fractures. Morover, it is associated with significant gastrointestinal distress and a painful lower extremity syndrome. Because of these factors, it has not been very popular in the treatment of osteoporosis (37).

Various combinations and treatment regimens of these drugs, as well as newer compounds such as synthetic parathyroid hormone, are currently undergoing extensive clinical trials. If their safety and efficacy are established, their use will be widespread.

REFERENCES

1. Melton LJ, Eddy DM, Johnston CC Jr. Screening for osteoporosis. Ann Int Med 1990;112:516-528.
2. Consensus Development Conference. Consensus development conference:diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 1993;94:646-650.
3. Kanis JA, Melton LJ, Christiansen C,et al. The diagnosis of osteoporosis. J Bone Miner Res 1994;9:1137-1146.
4. Browner WS, Pressman AR, Nevitt MC, et al. Mortality following fractures in older women. The study of osteoporotic fractures. Arch Intern Med 1996;156:1521-1525.
5. Looker AC, Orwoll ES, Johnston CC, et al. Prevalence of low bone density in older US adults from NHANES III. J Bone Miner Res 1997;12:1761-1769.
6. Melton LJ, Chrischilles EA, Cooper C, et al. How many women have osteoporosis? J Bone Miner Res 1992;7:1005-1007.
7. Nordin BEC, Need AG, Bridges A, Horowitz M. Relative contributions of years since menopause, age, and weight to vertebral density in postmenopausal women. J Clin Endocrinol Metab 1992;74:20-23.
8. Riis B, Thomsen K, Christiasen C. Does calcium supplementation prevent postmenopausal bone loss? A double-blind, controlled clinical study. N Engl J Med 1987;316:173-177.
9. Chetkowski RJ, Meldrum DR, Steingold KA, et al. Biologic effects of transdermal estradiol. N Engl J Med 1986;314:1615-1620.
10. Parisien M, Silverberg SJ, Shane E, et al. The histomorphometry of bone in primary hyperparathyroidism:Preservation of cancellous bone structure. J Clin Endocrinol Metab 1990;70:930-937.
11. Mosekilde L, Melsen F. A tetracycline-based histomorphometric evaluation of bone resorption and bone turnover in hyperthyroidism and hyperparathyroidism. Acta Med Scand 1978;204:97-101.
12. Rigotti NA, Nussbaum SR, Herzog DB, Neer RM. Osteoporosis in women with anorexia nervosa. N Engl J Med 1984;311:1601-1606.
13. Klibanski A, Biller BM, Schoenfeld DA, et al. The effects of estrogen administration on trabecular bone loss in young women with anorexia nervosa. J Clin Endocrinol Metab 1995;80:898-904.
14. Counts DR, Gwirtsman H, Carlsson LM, et al. The effects of anorexia nervosa and refeeding on growth hormone-binding protein, the insulin-like growth factors (IGFs), and the IGF-binding proteins. J Clin Endocrinol Metab 1992;75:762-767.
15. Grinspoon SK, Baum HB, Peterson S, Klibanski A. Effects of rhIGF-I administration on bone turnover during short-term fasting. J Clin Invest 1995;96:900-906.
16. Rosen HN. Primary biliary cirrhosis and bone disease. Hepatology 1995;21:253-259.
17. Riggs BL, Melton LJ. Involutional osteoporosis. N Engl J Med 1986;314:1676-1686.
18. Chapuy MC, Arlott ME,Duboeuf F,et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med 1992;327:1637-1642.
19. Ettinger B, Pressman A, Sklarin P, et al. Associations between low levels of estradiol, bone density, and fractures among elderly women: The Study of Osteoporotic Fractures.J Clin Endocrinol Metab 1998;83:2239-2243.
20. Cummings SR, Browner WS, Bauer D, et al. For the Study of Osteoporotic Fractures Research Group. Endogenous hormones and the risk of hip and vertebral fractures among older women. N Engl J Med 1998;339:733-738.
21. Prince RL, Smith M, Dick IM, et al. Prevention of postmenopausal osteoporosis: A comparative study of exercise,calcium supplementation, and hormone-replacement therapy. N Engl J Med 1991;325:1189-1195.
22. Genant HK, Cann CE, Ettinger B, Gordan GS. Quantitative computed tomography of vertebral spongiosa: A sensitive method for detecting early bone loss after oophorectomy. Ann Intern Med 1982;97:699-705.
23. Gallagher JC, Kable WT, Goldgar D. Effect of progestin therapy on cortical and trabecular bone: Comparison with estrogen. Am J Med 1991;90:171-176.
24. Kelepouris N, Harper KD, Gannon F, et al. Severe osteoporosis in men. Ann Intern Med 1995;123:452-460.
25. Behre HM, Kliesch S, Leifke E, et al. Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. J Clin Endocrinol Metab 1997;82:2386-2390.
26. Soule SG, Conway G, Prelevic GM, et al. Osteopenia as a feature of the androgen insensitivity syndrome. Clin Endocrinol 1995;43:671-674.
27. Slemenda CW, Longcope C, Zhou L, et al. Sex steroids and bone mass in older mass. Positive associations with serum estrogens and negative associations with androgens. J Clin Invest 1997;100:1755-1759.

28. Smith EP, Boyd J, Frank GR, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 1994;331:1056-1062.

29. Carani C, Qin K, Simoni M, et al. Effect of testosterone and estradiol in a man with aromatase deficiency. N Engl J Med 1997;337:91-95.

30. Slemenda C, Longcope C, Peacock M, et al. Sex steroids, bone mass and bone loss. J Clin Invest 1996;97:14-21.

31. Riggs BL. Vitamin D-receptor genotypes and bone density. N Engl J Med 1997;337:125-126.

32. Uitterlinden AG, Burger H, Huang Q, et al. Relation of alleles of the collagen type Ia I gene to bone density and the risk of osteoporotic fractures in postmenopausal women. N Engl J Med 1998;338:1016-1021.

33. Hopper JL, Seeman E. The bone density of female twins discordant for tobacco use. N Engl J Med 1994;330:387-392.

34. Bjarnason I, Macpherson A, Mackintosh C, et al. Reduced bone density in patients with inflammatory bowel disease. Gut 1997;40:228-233.

35. Liu B, Anderson G, Mittman N, et al. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. Lancet 1998;351:1303-1307.

36. Ensrud KE, Lipschutz MP, Cauley JA. Body size and hip fracture risk in older women: A prospective study. Am J Med 1997;103:274-280.

37. Kleerekoper M, Avioli LV. Evaluation and treatment of postmenopausal osteoporosis. In: Favus MJ, Ed. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism 2nd ed. Lippincott-Raven, Philadelphia, 1993:223-229.

38. Jackson JA. Osteoporosis in men. In: Favus MJ, Ed. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 2nd ed. Lippincott-Raven, Philadelphia, 1993:255-258.

39. Genant HK, Engelke K, Fuerst T, et al. Noninvasive assesment of bone mineral and structure: State of the art. J Bone Miner Res 1996;11:707-712.

40. Dawson-Hughes B, Dallal GE, Krall EA, et al. Controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. N Engl J Med 1990; 323:878-883.

41. Recker RR, Davies KM, Dowd RM, Heany RP. The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. Ann Int Med 1999; 130:897-904.

42. Khouidhunkit W, Shoback DM. Clinical effects of raloxifene hydrochloride in women. Ann Int Med 1999;130:431-439.

43. Avioli LV. Heterogeneity of osteoporotic syndromes and the response to calcitonin therapy. Calcific Tissue Int 1991;49 (Suppl 2): S16-19.

44. Tilyard MW, Spears GFS, Thompson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. N Engl J Med 1992; 326:357-361.

45. Wimalawansa SJ. Combined therapy with estrogen and etidronate has an additive effect on bone mineral density in the hip and vertebrae: Four year randomized study. Am J Med 1995;99:36-42.

46. Karpf DB, Shapiro DR, Seeman, et al. Prevention of nonvertebral fractures by alendronate. A metaanalysis. JAMA 1997; 277:115-121.