

Evaluation and Treatment of Postmenopausal Osteoporosis

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Osteoporosis is a prevalent condition among elderly women and is associated with an increased risk for fractures. With the burgeoning size of the elderly population, a practitioner is likely to face many questions regarding the evaluation and management of postmenopausal osteoporosis. This review discusses and compares available therapies. All women should have adequate calcium and vitamin D intake. Women diagnosed as having osteoporosis should be evaluated for secondary causes of osteoporosis and risk factors for falls. For women with postmenopausal osteoporosis, therapy with hormone replacement, bisphosphonates (alendronate sodium or risedronate sodium), raloxifene hydrochloride, or calcitonin should be considered. The results of ongoing studies will help refine the strategies used for management of postmenopausal osteoporosis.

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Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.¹ Approximately 9.4 million postmenopausal white women in the United States have osteoporosis, of which 4.8 million have already experienced a fracture.² In 1995, healthcare costs related to osteoporotic fractures were estimated to be \$13.8 billion.³

Furthermore, as baby boomers reach age 65 years, the number of older people in the United States will increase during the next 30 years. In 1999, there were 34.5 million persons 65 years or older, representing 12.7% of the US population. By 2030, there will be an estimated 70 million older persons.⁴ Thus, age-related problems such as osteoporosis will continue to be a substantial health concern for the coming decades.

... PHYSIOLOGICAL AND CLINICAL CONSIDERATIONS OF EARLY AND LATE POSTMENOPAUSAL OSTEOPOROSIS ...

In 1983, Riggs and Melton^{5,6} proposed that involutional or primary osteoporosis could be divided into type I (postmenopausal osteoporosis) and type II (age-related or senile osteoporosis). Although oversimplified and overlapping, this classification scheme helps explain some of the physiological changes that occur in bone with aging. Type I postmenopausal osteoporosis is characterized by accelerated bone loss in the early postmenopausal period and is related to estrogen deficiency. Estrogen seems to control the local production of bone-resorbing cytokines and other factors.⁷ Reduced estrogen levels seem to result in increased responsiveness or production of paracrine mediators (eg, interleukin 1) that activate osteoclasts and bone resorption. Bone also becomes more sensitive to the bone-resorbing effects of parathyroid hormone (PTH) in the setting of reduced estrogen levels. The mobilization of calcium from bone tends to suppress serum PTH levels. Increased urinary calcium losses and reduced gastrointestinal tract calcium absorption maintain serum calcium at normal levels.⁶ The rapid bone loss characterizing type I osteoporosis usually occurs at a rate of 1% to

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2% per year but can be as high as 5%. In general, this phase lasts 4 to 8 years. Cancellous bone is primarily affected. Therefore, the spine in particular is affected and becomes susceptible to compression fractures.

The second phase of bone loss occurs 10 to 20 years after menopause (late menopause) and is associated with more gradual loss of bone (0.5%-1.0% per year). Both men and women are affected, and losses of both cancellous and cortical bone are seen. During this phase, referred to as type II osteoporosis (age-related or senile osteoporosis), a variety of age-related alterations in calcium metabolism result in secondary hyperparathyroidism.⁸ Although generally remaining within the reference range, PTH levels tend to increase. This increase has been attributed to the age-related decline in renal function, intestinal malabsorption of calcium, and altered vitamin D metabolism. The rise in PTH levels results in increased bone turnover. Thus, in this setting, the circulating calcium concentration is maintained at the expense of bone. Bone is further lost as a result of senescent changes in osteoblast function, causing reduced bone formation.^{9,10}

... FRACTURE RISK AND THE DIAGNOSIS OF OSTEOPOROSIS ...

In 1994, the World Health Organization convened a consensus panel and published guidelines for diagnosing osteoporosis based on an individual's bone mineral density (BMD) according to the T score (Table 1).¹¹ The T score is the number of SDs above or below the mean BMD at peak bone mass or at age 30 years. There is a direct correlation between BMD

and risk for a fragility or osteoporotic fracture. For vertebral BMD, each 1 SD below peak BMD is associated with a 2-fold increased risk for vertebral fractures.¹² In white women older than 65 years, each 1 SD decrease in femoral neck BMD increases the age-adjusted risk for hip fracture by 2.6 (95% confidence interval [CI], 1.9-3.6).¹³

Bone mineral density is used to define osteoporosis, primarily because BMD is the most powerful predictor of fracture risk. The ability of BMD to predict future fractures equals the ability of other common screening tools, such as cholesterol levels and blood pressure, to predict cardiovascular events. Although risk factors for low BMD can be elicited from the medical history, such information only identifies approximately 60% of those with low BMD.¹⁴

Additional factors that are independently related to fracture risk include a preexisting fragility fracture (associated with a 5-fold risk of subsequent fracture),¹⁵⁻¹⁷ advancing age,¹⁸ maternal history of hip fracture,¹⁹ use of certain medications, sedentary lifestyle,¹⁹ small body size (<58 kg),²⁰ presence of other comorbid conditions (eg, falls, dementia, and parkinsonism), and reduced functional status.²¹ Therefore, fracture risk assessment must consider individual patient factors in addition to BMD.

... ASSESSMENT OF BMD ...

Although different techniques are available to measure bone mass, dual-energy X-ray absorptiometry (DEXA) is generally the method of choice. It is quick, has low X-ray exposure, and can measure mass at the spine, hip, or radius (or other sites) with good precision. Portable machines are available that measure only peripheral sites, such as the calcaneus or distal radius.

Peripheral machines may provide some screening utility. However, their routine use and role in allowing the physician to diagnose and treat patients is limited for several reasons. First, although measurement of low BMD at any skeletal site is predictive of fracture risk, the most accurate determination of site-specific risk is measurement at the site of interest. For example, measuring the spine gives the

Table 1. World Health Organization Guidelines for the Diagnosis of Osteoporosis

Category	BMD in Relation to Peak BMD	T Score
Normal bone mass	< 1 SD below peak	> -1
Osteopenia	1.0-2.5 SD below peak	-1 to -2.5
Osteoporosis	≥2.5 SD below peak	≤-2.5
Established osteoporosis	≥2.5 SD below peak in the setting of at least 1 fragility fracture	≤-2.5

BMD = bone mineral density.

most sensitive and specific values for predicting spinal fractures. In 50-year-old women, radial BMDs at the 10th and 90th percentiles are correlated with estimated lifetime risks of hip fracture of 19% and 12%, respectively. In contrast, the same percentile determinations made at the hip correspond to lifetime risks of 25% and 8%, respectively.^{13,22} In addition, discordance of measurements may occur, ie, in some individuals distal radius BMD may be normal but spine BMD may be low.²³ Second, the site of distribution of low BMD can be used to identify the cause of bone loss. For example, low BMD of the wrist and hip but preserved BMD of cancellous sites, such as the vertebrae, is the pattern of cortical bone loss seen in primary hyperparathyroidism. With corticosteroid use, rapid bone loss (≤ 6 months) occurs predominantly at the spine, so monitoring the wrist would be inappropriate. Third, the ability to monitor the response to a therapeutic intervention generally requires measurement of axial sites, as most therapeutic interventions have little or no effect at the wrist. Last, virtually all recent studies have monitored response to therapy by using table DEXA machines, and, therefore, other technologies currently have little known value in monitoring patients.

The frequency of BMD measurements is also a common issue of debate. For a “real” change in BMD to occur, the difference in repeated measurements should be ≥ 2.8 times the coefficient of variation of the measuring technique used.²³ For DEXA, the coefficient of variation at the spine is usually 1.0. Therefore, a change of at least 2.8% or greater between measurements is necessary to assume significance. In general, bone mass should not be measured more frequently than every 2 years. One exception is for patients beginning a course of long-term corticosteroids, when significant bone loss may occur early in the treatment. In these individuals, measurements at baseline and after 6 months of medication use are appropriate. There is considerable debate over which single skeletal site is optimal to measure. Most evidence for fracture reduction from current pharmacologic interventions is based on studies measuring changes in lumbar BMD and effects on spinal fractures.²⁴⁻²⁹ There is much less experimental data showing that pharmacologic interventions prevent hip fractures. Furthermore, only small changes in bone mass occur at the hip. Measurements at the hip have the advantage of fewer factors potentially complicating interpretation. In older patients, osteophytes or vascular calcifications can cause measurements at the spine to

be artificially elevated. Therefore, some investigators²³ suggest the femoral neck or total hip as a preferable site for measuring BMD in patients older than 70 years.

Patients at risk for osteoporosis should have BMD measured (**Table 2**). In addition, as of July 1, 1998, Medicare Part B includes coverage for bone mass measurements for 5 specific groups: estrogen-deficient women at clinical risk for osteoporosis, individuals with vertebral abnormalities as shown on plain radiography, individuals receiving or planning to receive long-term glucocorticoid therapy, those with primary hyperparathyroidism, and individuals being monitored to assess the response to or efficacy of a Food and Drug Administration (FDA)-approved osteoporosis drug therapy. Furthermore, measurements must be performed by techniques or devices approved by the FDA, and Medicare covers testing performed every 2 years, or more frequently if medically necessary.

... FURTHER PATIENT EVALUATION ...

Once a diagnosis of osteoporosis is made, a thorough history, a physical examination, and directed diagnostic studies should be performed to identify modifiable risk factors and to exclude “secondary” causes of osteoporosis (**Table 3**). Assessment should also include a review of dietary calcium intake, a fracture history, a drug use history (eg, alcohol, anti-convulsant, corticosteroid, and tobacco use), and a family history of osteoporosis. Factors that increase

Table 2. Indications for Bone Mineral Density Measurements

■ Estrogen deficiency
■ Women aged >65 y
■ Suspected osteopenia on plain radiography
■ Fragility fracture on plain radiography
■ Asymptomatic primary hyperparathyroidism
■ Long-term use of glucocorticoids
■ Management of patients after organ transplantation
■ Evaluation of the effects of a prescribed intervention on bone mass

the risk for falls, such as medication use, unsteady gait,³⁰ and sedentary lifestyle,²¹ should also be reviewed.

The laboratory evaluation should include a complete blood cell count, a serum electrolyte count (including calcium and phosphorus), and creatinine, total protein, albumin, and liver enzyme (including alkaline phosphatase) measurements. In patients with primary osteoporosis, these values will be normal. Thyroid-stimulating hormone concentration should also be measured. In some situations, a serum intact PTH and serum protein electrophoresis should be considered if secondary hyperparathyroidism or multiple myeloma is a consideration (for example, older patients in the former situation or those with elevated total protein levels or other evidence of multiple myeloma). If

impaired calcium absorption is suspected, a 24-hour urine calcium measurement can be helpful. Values should be ≥ 100 mg/d (reference range, 100-200 mg/d). 25-hydroxyvitamin D₃ is used to assess for vitamin D deficiency but is not routinely indicated. Biochemical markers of bone turnover, such as N-telopeptide in the diagnosis and management of osteoporosis, are not routinely indicated at present.

In addition, a lateral radiograph of the thoracic and lumbar spine should be considered in patients undergoing evaluation. The presence of a spinal compression fracture, many of which are asymptomatic, greatly increases the likelihood of future fractures and may help in deciding whether to initiate therapy in an individual patient. The number needed to treat to prevent a subsequent fracture is much reduced when patients from clinical studies have been analyzed comparing those with prevalent fractures versus those without existing fractures.^{29,31}

Table 3. Risk Factors for Bone Loss and Secondary Causes of Osteoporosis

<ul style="list-style-type: none"> ■ Lifestyle and nutrition <ul style="list-style-type: none"> Prolonged amenorrhea Diet low in calcium Minimal sun exposure Smoking Excessive alcohol intake Inactivity or prolonged immobilization Prolonged parenteral nutrition Low body weight ■ Medical conditions <ul style="list-style-type: none"> Ankylosis spondylitis Anorexia nervosa Chronic obstructive lung disease Chronic renal failure Cushing's syndrome Inflammatory bowel disease Malabsorption secondary to gastrointestinal tract or hepatobiliary disease Mastocytosis Multiple myeloma Osteogenesis imperfecta Posttransplantation Primary hyperparathyroidism Primary hypogonadism Rheumatoid arthritis Thyrotoxicosis ■ Medication use <ul style="list-style-type: none"> Long-term corticosteroid therapy (≥ 7.5 mg/d of prednisone for >6 mo) Excessive thyroid replacement Chemotherapy Gonadotropin-releasing hormone agonist or antagonist Phenytoin and phenobarbital
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... THERAPEUTIC AND MANAGEMENT CONSIDERATIONS ...

How to treat patients at risk for or with primary osteoporosis depends on the individual patient and his or her clinical circumstances. The issues pertaining to a perimenopausal woman are different from those related to an 80-year-old woman. Furthermore, diet, exercise, and fall prevention counseling should be part of the management of all patients with osteoporosis. The following is a summary of therapies currently available.

Calcium

Adequate calcium and vitamin D intake are critical for bone health at all ages. Calcium supplementation is important in maintaining BMD during menopause but, by itself, does not seem to be as effective as estrogen during the early postmenopausal period (first 5 years).³² Calcium supplementation can eliminate bone loss in osteoporotic patients and healthy older patients.³³⁻³⁸ The lack of efficacy in blocking bone resorption noted in some trials^{34,37} may be related to dose and bioavailability of the form used.³⁹ The provision of modest doses of calcium and vitamin D to elderly nursing home patients with marginal intake of these nutrients resulted in an abrupt decrease in fractures.⁴⁰ In ambulatory older patients (>65 years), calcium and vitamin D supplementation also decreased fractures.³⁹ In a 4-year randomized trial reported by Riggs et al,⁴¹ supplementing older ambulatory

women (mean age, 66 years; range, 61-70 years) without osteoporotic fractures with calcium citrate (1600 mg/d) vs placebo maintained BMD at the lumbar spine and proximal femur. Serum PTH and urinary free pyridinoline levels were reduced, suggesting that age-related increases in bone turnover were reduced with calcium supplementation.

By reducing PTH-mediated bone resorption and decreasing bone turnover, calcium acts as an antiresorptive agent. The adequate provision of calcium is important when administering other bone-active agents and should not be overlooked.

Women (and men) older than 65 years should consume at least 1500 mg of calcium and 600 to 800 IU of vitamin D.⁴²⁻⁴⁴ In the elderly, calcium citrate may have an advantage over other calcium salts because of greater bioavailability and apparent effectiveness in maintaining bone mass at axial and appendicular skeletal sites.^{37,39} It can also be taken with or without food because its absorption is independent of gastric acid secretion. Calcium carbonate should be taken with meals because its absorption requires acidity for optimal absorption.

Estrogen

Estrogen is an antiresorptive agent that inhibits osteoclastic activity and is indicated for the prevention and management of osteoporosis. It is well known that estrogen maintains or increases bone mass. Because unopposed estrogen increases the risk for endometrial cancer, women who have not undergone a hysterectomy should concurrently take progesterone to reduce this risk. Several studies⁴⁵⁻⁴⁷ have shown that the addition of progesterone does not attenuate the bone effects of estrogen. The lowest effective dose of oral conjugated equine estrogen (CEE) that preserves BMD is 0.625 mg daily.⁴⁸ Transdermal estrogen administration also has beneficial effects on BMD.⁴⁹

More recent studies have evaluated use of CEE (0.3 mg/d) in early (<4 years)⁵⁰ and late⁵¹ menopause. In a randomized, 2-year trial, Genant et al⁵⁰ studied early postmenopausal women with normal baseline spine BMD and compared 2 doses of unopposed estrogen. Patients also received 1000 mg/d of calcium citrate or calcium carbonate. In an intention-to-treat analysis, spine BMD increased by 1.76% with use of estrogen, 0.3 mg/d; increased by 2.80% with use of estrogen, 0.625 mg/d; and decreased by 2.52% in the placebo group.

In a randomized, placebo-controlled trial, Recker et al⁵¹ studied the effects of low-dose estrogen therapy in elderly white women (mean age, ≈73

years). Their lumbar spine T scores were between -1.7 and -3.7. If necessary, participants received calcium supplements to raise their daily intake to ≥1000 mg/d and vitamin D supplements to raise their serum 25-hydroxyvitamin D levels to ≥75 nmol/L (30 ng/mL). The treatment group received combined CEE (0.3 mg/d) and medroxyprogesterone acetate (2.5 mg/d). In a 3.5-year intention-to-treat analysis, there was a statistically significant 3.2% increase in spine BMD vs no significant change with calcium and vitamin D intake alone. Among patients who were more than 90% compliant with therapy, the increase was 5.2%.

When estrogen therapy was compared with alendronate sodium therapy in a randomized, controlled trial⁵² involving women in late menopause, there was no difference between groups in the gain in vertebral BMD at 24 months.

Evidence supporting the beneficial effect of estrogen therapy on fracture rates is derived primarily from observational studies, which reveal several consistent findings. Most studies suggest that early and continued use of estrogen is most effective in maintaining bone mass and preventing fractures.^{53,54} There is less certainty of its efficacy after age 70,⁵⁵⁻⁵⁸ and although the highest incidence of hip fractures occurs among individuals 80 years and older, few studies have included this age group.

It is likely that women will carefully consider the risks and benefits of estrogen replacement, especially given the controversy concerning breast cancer risk and the results of the Heart and Estrogen/Progestin Replacement Study,⁵⁹ which showed no benefit for secondary prevention of cardiovascular disease. The Women's Health Initiative Study,⁶⁰ which includes a trial of 69,000 women randomized to receive placebo or hormone replacement therapy, will hopefully provide more definitive answers by the end of this decade. Currently, the primary role of estrogen replacement therapy is for the prevention of osteoporosis and for decreasing menopausal symptoms.

Nasal Salmon Calcitonin

Calcitonin is an endogenous hormone that inhibits the production and activity of osteoclasts, thereby preventing bone resorption. Nasal salmon calcitonin is approved for use in women with postmenopausal osteoporosis ≥5 years after the start of menopause. The recommended dose is 200 IU/d intranasally.

In multiple trials, nasal calcitonin use has had a modest effect in maintaining bone mass in the spine,

with little or no effect at the hip or forearm. Recently, Chesnut et al⁶¹ reported results from the Prevent Recurrence of Osteoporotic Fractures study, a large multicenter trial evaluating the effect of administering various doses of nasal calcitonin on the risk of new vertebral fractures in women with preexisting osteoporotic fractures. Overall, this 5-year study did not show a significant reduction in recurrent fractures or BMD differences. In a subgroup of patients receiving 200 IU of calcitonin daily, a significant 33% reduction in new vertebral fractures was found. There was no reduction in fractures, however, in women who received 100 or 400 IU and no change in BMD, suggesting a lack of dose response. The study was potentially biased by a 59% dropout rate, and investigators were not masked to BMD results (a key outcome).

Calcitonin has been shown to have an analgesic effect.^{62,63} There are a variety of proposed mechanisms for this effect, including central opioid properties; however, neither the exact mechanism nor the true clinical efficacy is known. Some experts recommend a 1-week trial for patients with an acute fracture in an attempt to decrease pain. If there is no relief, medication use can be discontinued.

Bisphosphonates

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption.^{64,65} They are analogs of pyrophosphate but are resistant to enzymatic hydrolysis. There are currently 2 approved bisphosphonates for the prevention and treatment of osteoporosis: alendronate and risedronate sodium. Both agents are effective in maintaining or increasing BMD at the spine and hip in the perimenopausal period and in women with osteoporosis. They have also been shown to decrease the risk of fractures in patients with osteoporosis.

The ability of alendronate to prevent bone loss was assessed in women younger than 60 years in the Early Postmenopausal Intervention Cohort Study.⁶⁶ Compared with placebo, use of alendronate (5 mg/d) prevented bone loss at the lumbar spine and hip but not at the distal forearm.

Liberman et al²⁴ conducted a multinational, multicenter dose-comparison trial of alendronate vs placebo in osteoporotic patients (lumbar spine T score, -2.5 or less; 20% had baseline vertebral fractures; mean age, 64 years). All participants received 500 mg of calcium. At 36 months, the 10-mg/d dose increased lumbar spine BMD by 8.8% and femoral neck BMD by 5.9% compared with placebo ($P < .001$). Alendronate therapy resulted in a 48% reduc-

tion in vertebral fractures (6.2% placebo vs 3.2% alendronate; relative risk reduction [RRR], 48%; and absolute risk reduction [ARR], 3%).

The Fracture Intervention Trial (FIT)²⁵ evaluated the effects of alendronate therapy on bone mass and fractures in osteoporotic women (femoral neck BMD T score, less than -2.1 ; age, 54-81 years). Two groups, one with and one without vertebral fractures, were studied. Black et al²⁵ published results from the group of 2027 women with baseline vertebral fractures. The initial dose of alendronate (5 mg/d) was increased to 10 mg/d after 24 months, when the study sponsor determined greater efficacy at the higher dose.²⁵ At the originally defined endpoint of 36 months, bone mass had increased 6.2% at the lumbar spine and 4% at the femoral neck in the alendronate group compared with the placebo group. The risk of new vertebral fractures, the primary endpoint, was 47% lower in the alendronate group than in the placebo group ($P < .001$). The relative hazards (RH) for hip fracture for alendronate versus placebo was 0.49 (95% CI, 0.23-0.99).

In FIT participants with no baseline vertebral fracture, 4432 women were followed up for an average of 4.2 years.²⁶ In subgroup analysis, treatment with alendronate decreased the incidence of vertebral fractures by 44% (3.8% in the placebo group vs 2.1% in the alendronate group; RRR, 44%; ARR, 1.7%). The greatest impact occurred in those with the lowest BMD. The number needed to treat increased from 35 in women with femoral neck BMD T scores less than -2.5 , to 59 for those with T scores of -2.5 to -2.0 , and to approximately 363 for those with T scores of -2.0 to -1.6 . Results of post-hoc analysis showed that alendronate treatment significantly reduced hip fractures only in women with a femoral neck T score of -2.5 or less (2.2% vs 1.0%; RH 0.44, 95% CI, 0.18-0.97).

Risedronate, another bisphosphonate, is effective at maintaining bone mass and decreasing bone turnover markers in early postmenopausal women with normal bone mass and in early and late postmenopausal women with low bone mass. Furthermore, 2 large-scale trials, one in North America²⁷ and one in Europe,²⁸ evaluated the effect of risedronate use on the incidence of fractures in women with previous vertebral fractures. In the North American trial,²⁷ 939 women with at least 1 vertebral fracture at baseline were studied for 3 years. Treatment with risedronate (5 mg/d) resulted in a significant 41% reduction (95% CI, 18%-58%) in new vertebral fractures (16.3% in the placebo group vs 11.3% in the risedronate group; RRR, 41%; ARR,

5%).²⁷ The European trial²⁸ evaluated 1226 women with at least 2 vertebral fractures at baseline and found similar results. Risedronate therapy (5 mg/d) decreased new vertebral fractures by 49% (95% CI, 27%-64%; incidence, 29% in the placebo group vs 18% in the risedronate group; ARR, 11%; RRR, 49%) after 3 years of therapy.²⁸ In contrast to alendronate studies, individuals were not excluded because of previous or active gastrointestinal tract illness or because of concomitant use of aspirin or nonsteroidal anti-inflammatory medications. The incidence of gastrointestinal tract adverse effects was similar in the placebo and risedronate groups.

In a recent study by McClung et al³¹ evaluating the effect of risedronate therapy on the incidence of hip fractures (primary outcome) in elderly women, patients received risedronate for 3 years. Risedronate use was effective at reducing hip fractures in women aged 70 to 79 years who had femoral neck BMD T scores less than -3 (ARR, 1.3%; RRR, 40%); however, among women 80 years and older, the majority of whom were enrolled on the basis of a nonskeletal risk factor for hip fracture (eg, poor gait), risedronate administration had no effect on fracture ($P = .35$).

Some studies have evaluated the use of combined bisphosphonate and estrogen. Bone et al⁵² examined the effect of combining alendronate and estrogen use. In their study of 425 postmenopausal women with low bone mass, patients were randomized to 1 of 4 treatments: alendronate, 10 mg/d; CEE, 0.625 mg/d; combination alendronate and CEE; or placebo. All patients received daily supplements of 500 mg of calcium. Mean age in each group was approximately 62 years. Compared with baseline, lumbar spine and femoral neck BMDs at 24 months were both decreased by 0.6% in the placebo group; increased by 6% and 2.9%, respectively, in the alendronate-only group; and increased by 6% and 2.6%, respectively, in the estrogen-only group. Use of combined alendronate and estrogen increased spine BMD by 8.3% and femoral neck BMD by 4.2%. Bone turnover markers were suppressed in all treatment groups. Whether the small increase in BMD seen with combined therapy has an impact in fracture reduction is not known. A reduction in fracture risk should be demonstrated before routine use of both agents is considered.

Because bisphosphonates are associated with low bioavailability and an increased risk for esophagitis, it is recommended that patients take the medication on an empty stomach, with 8 oz of water, and that

they remain in an upright position for at least 30 minutes after swallowing the tablet. The medication is contraindicated in patients with dysphagia or esophageal stricture.

The prevention dose for women who have a normal BMD or a T score that fulfills the criteria for osteopenia is 5 mg/d for both alendronate and risedronate. The treatment dose used in women with established fractures or with a BMD that fulfills the criteria for osteoporosis is 10 mg/d for alendronate and 5 mg/d for risedronate. The long duration of action of bisphosphonates allows for less frequent dosing,⁶⁷ and the FDA has recently approved alendronate for once-a-week dosing: 35 mg for prevention and 70 mg for treatment.

Raloxifene Hydrochloride

Selective estrogen receptor modulators have been developed to avoid the breast and uterine tissue effects associated with estrogen. Raloxifene is the first selective estrogen receptor modulator approved for the prevention and treatment of osteoporosis. In addition to its antiresorptive activity at the bone, raloxifene lowers low-density lipoprotein cholesterol levels and has either antagonistic or neutral activity against breast and uterine tissue.⁶⁸ Use of raloxifene (60 mg/d) prevents perimenopausal bone loss.⁶⁸

The Multiple Outcomes of Raloxifene Evaluation trial²⁹ was designed to examine the effects of raloxifene on bone. Two groups were enrolled: (1) patients with osteopenia and at least 1 moderate-severe or at least 2 mild vertebral fractures and (2) patients with osteoporosis of the hip or spine. Primary endpoints included new vertebral fracture and BMD changes. Any nonvertebral fracture was a secondary endpoint. This study followed 7705 postmenopausal women (mean age, 67 years) for 3 years. All women received daily supplements of 500 mg of calcium and 400 to 600 IU of cholecalciferol. Compared with placebo, use of raloxifene at 60- and 120-mg/d doses resulted in femoral neck BMD that was greater by 2.1% and 2.4%, respectively, and spine BMD that was higher by 2.6% and 2.7%, respectively. In women with or without previous vertebral fractures, raloxifene use reduced the incidence of vertebral fractures by 30% (95% CI, 20%-50%; incidence, 10.1% in the placebo group vs 6.6%) in the 60-mg/d raloxifene group (ARR, 3.5%; RRR, 30%) and by 50% (95% CI, 30%-60%; incidence, 10.1% in placebo vs 5.4%) in the 120-mg/d group. The number needed to treat to prevent vertebral fractures was 42 in women with at least 1 vertebral

fracture and 113 in those with no previous fracture. There was no difference between the raloxifene and placebo groups in the incidence of nonvertebral fractures, including hip fractures.

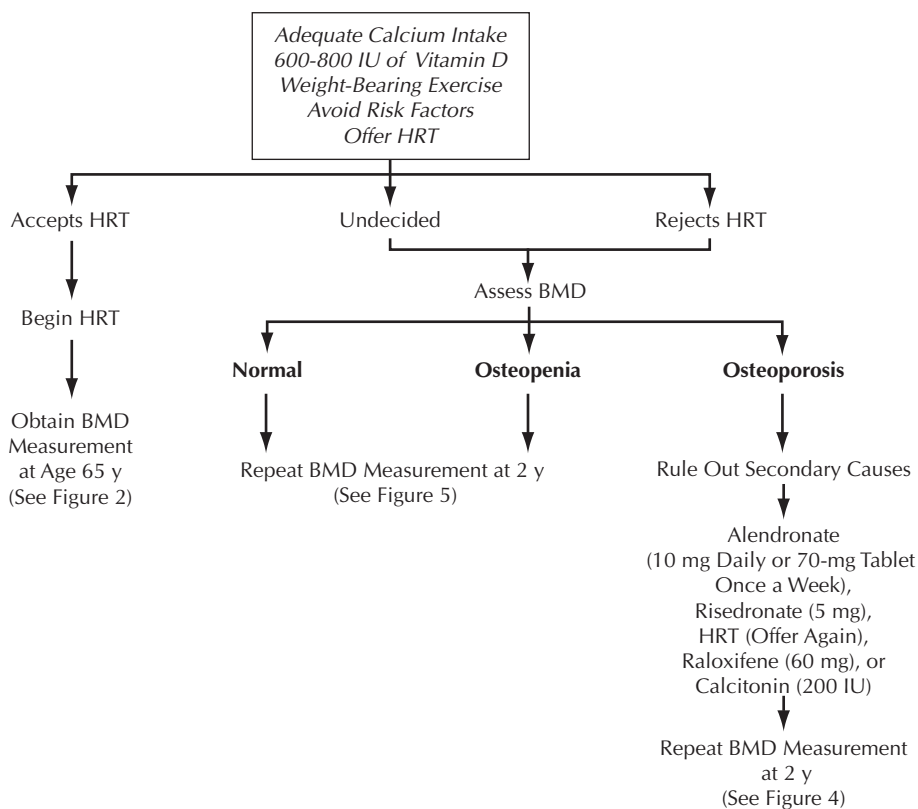
Despite its improved adverse-effect profile over estrogen therapy, with decreased breast and uterine stimulation, raloxifene use is still associated with thromboembolic disease. In the Multiple Outcomes of Raloxifene Evaluation trial,²⁹ the increased relative risk for venous thromboembolism was 3.1 (95% CI, 1.5-6.2), which is similar to the 3-fold risk seen with estrogen therapy. The package insert recommends discontinuation of raloxifene administration at least 72 hours before or during prolonged immobilization, and only after the patient is fully ambulatory should medication use be resumed. Importantly, raloxifene is ineffective in treating vasomotor symptoms. The treatment dose for raloxifene is 60 mg/d.

... CLINICAL APPLICATION ...

Algorithms for the management of osteoporosis are found in Figures 1 through 5. Osteoporosis risk factors include increasing age, history of maternal fracture, cigarette smoking, excessive alcohol use, and low body mass. In all women, adequate calcium and vitamin D intake should be ensured. Exercise helps to increase mobility and decrease risk of falls, whereas, specifically, weight-bearing exercises may improve bone mass. In addition, efforts should be made to avoid osteoporosis risk factors that can be modified. Risks for falls should also be assessed and modified. Figure 1 is the algorithm for postmenopausal women younger than 65 years without risk factors. Women without risk factors and with a BMD that fulfills the criteria for normal BMD or osteopenia can be followed with calcium and vitamin D alone. If osteoporosis is diagnosed based on a T score less than -2.5, secondary causes should be assessed and treatment begun. Prevention therapy should be considered in postmenopausal women younger than 65 years with risk factors or women older than 65 years (Figure 2) if their BMD fulfills the criteria for normal BMD or osteopenia. Treatment therapies should be instituted in women with BMDs that fulfill the criteria for osteoporosis.

If a woman is receiving treatment for osteoporosis and her BMD is less than -2.5 but her BMD was not assessed before instituting therapy (Figure 3), consider measuring urine concentration of N-telopeptide to determine whether she is responding to the therapy. N-telopeptides are markers of bone turnover that should decrease when bone resorption is inhibited. Efficacy of antiresorptive agents is reflected by a 24-

Figure 1. Algorithm for the Management of Postmenopausal Women Younger Than 65 Years Without Risk Factors for Osteoporosis



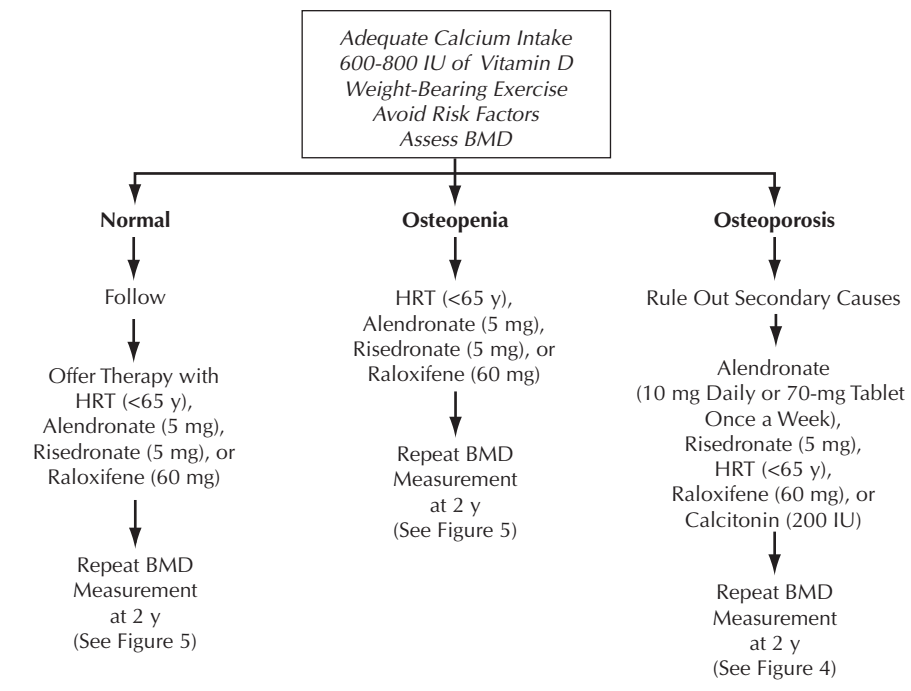
HRT = hormone replacement therapy; BMD = bone mineral density.

hour urine N-telopeptide concentration of <38 nM bone collagen equivalents (BCE)/mMCr.⁶⁹ If the concentration of the N-telopeptide is <38 nM BCE/mMCr, therapy is probably adequate and BMD should be assessed in 2 years without adding another therapy. If, however, the concentration of the N-telopeptide is increased (>38 nM BCE/mMCr), compliance should be assessed, secondary causes evaluated, and consideration given to adding another therapeutic agent or changing the therapy.

If therapy for osteoporosis is initiated, efficacy should be confirmed by another BMD measurement in 2 years (Figure 4). Additional measurements using the same densitometer are likely to yield more accurate results of clinically significant changes in BMD.

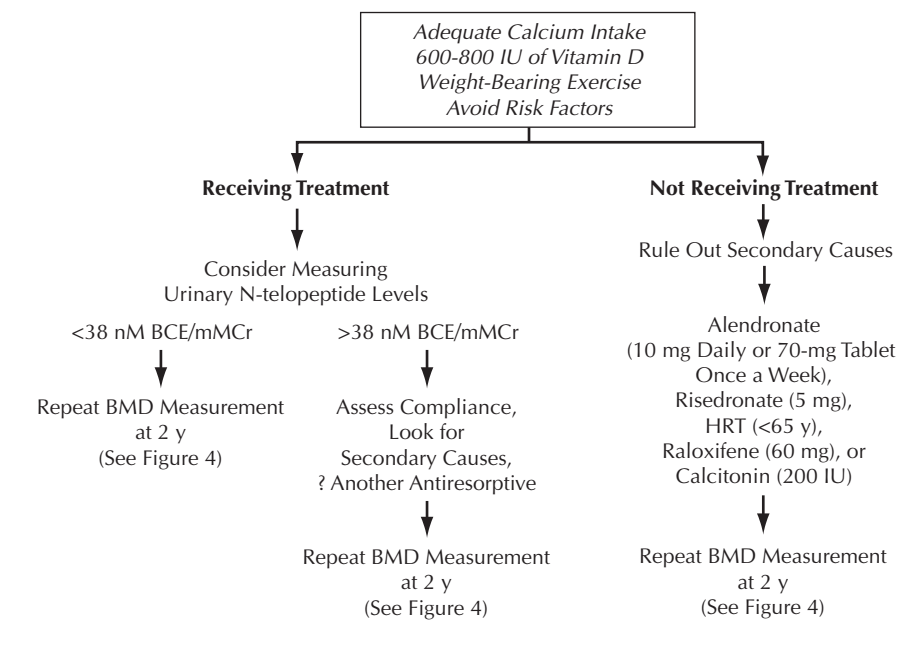
If a woman has a history of a normal BMD or one that fulfilled the criteria for osteopenia, BMD should be reassessed (Figure 5). If there is no change in the BMD with time or a documented increase, no changes are necessary. However, if BMD has decreased significantly (>3% or 2.8 times the coefficient of variation), therapy should be instituted or compliance assessed, secondary causes evaluated, and addition of another therapeutic agent or a change of therapy considered.

Figure 2. Algorithm for the Management of Postmenopausal Women Younger Than 65 Years with Risk Factors for Osteoporosis or Older Than 65 Years



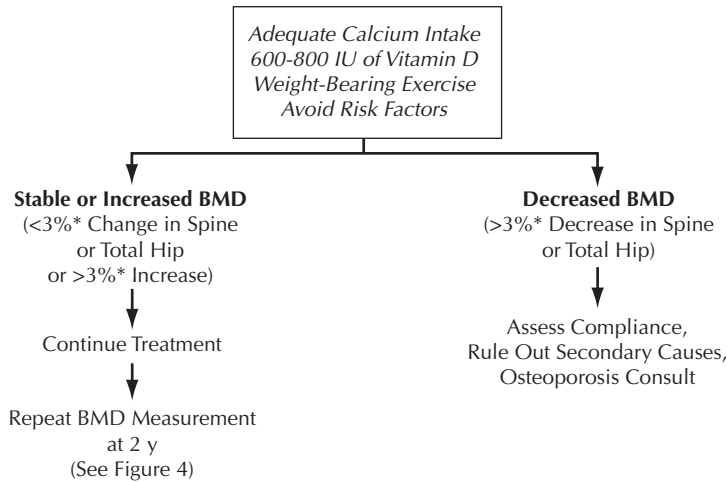
BMD = bone mineral density; HRT = hormone replacement therapy.

Figure 3. Algorithm for the Management of Postmenopausal Women with Established Osteoporosis or Fractures and No Previous BMD Measurement



BMD = bone mineral density; HRT = hormone replacement therapy.

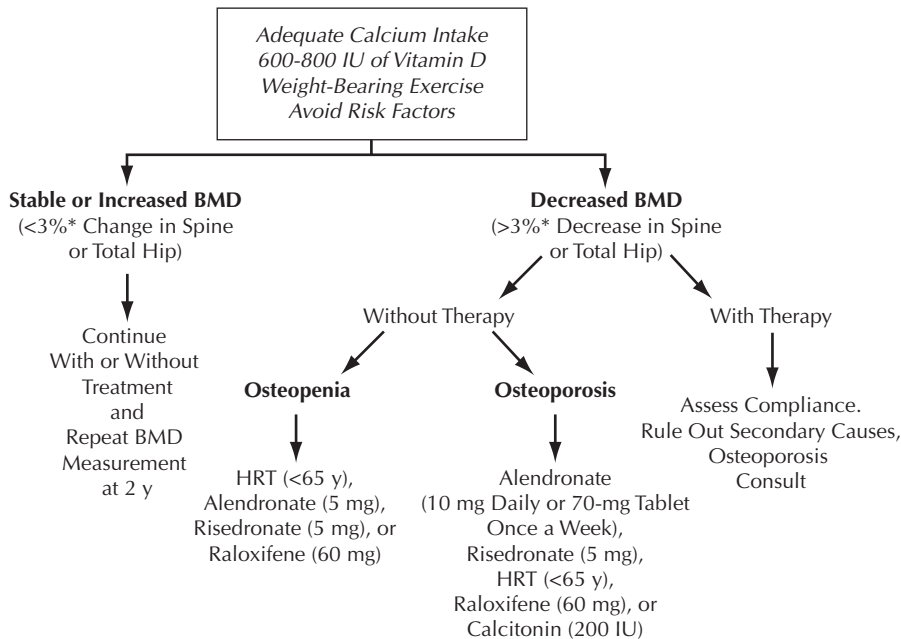
Figure 4. Algorithm for the Management of Postmenopausal Women with Established Osteoporosis or Fractures and Who Have Undergone Previous BMD Measurement and Are Receiving Treatment



*Or 2.8 times the coefficient of variation determined for a particular machine and body site measured.

BMD = bone mineral density.

Figure 5. Algorithm for Repeated BMD Measurement in Postmenopausal Women with a History of Normal or Low BMD With or Without Prevention Therapy



*Or 2.8 times the coefficient of variation determined for a particular machine and body site measured.

BMD = bone mineral density; HRT = hormone replacement therapy.

... SUMMARY ...

Osteoporosis is a prevalent condition among elderly women. Patients should be evaluated to rule out secondary causes of osteoporosis before treatment decisions are considered. In addition to a BMD measurement, other risk factors for fracture should be assessed and modified when possible. Adequate calcium and vitamin D intake should be ensured before considering additional pharmacological approaches. Osteoporosis therapy should be strongly considered in patients with osteoporosis, especially those with prevalent fractures, because these individuals are at greatest risk for recurrent fractures and are most responsive to treatment.

Interventions should be selected based on individual patient characteristics and not a broad "one size fits all approach." For example, estrogen therapy would be appropriate in an early postmenopausal woman with vasomotor symptoms and without a history of breast cancer. However, use of a bisphosphonate would be more appropriate for a 75-year-old woman with established osteoporosis. Clinicians now have a variety of agents from which to choose for the management and treatment of osteoporosis, and results from current studies will help refine the strategies for osteoporosis management.

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