Postmenopausal osteoporosis is associated with significant morbidity, mortality, reduction in quality of life, and increasing health care costs. It is estimated that 1.5 million women in the United States have one or more osteoporosis-related fractures annually. Fractures may occur at any site, but vertebral fractures are the most common. Longitudinal studies have demonstrated a decreased life expectancy associated with both vertebral and nonvertebral fractures. Once an initial fracture occurs, there is a fivefold increased risk of a second fracture within 1 year. The management of osteoporosis today incorporates multiple modalities of therapy. In addition to early detection, patient education, exercise, and nutritional supplementation, multiple therapeutic agents should be implemented early in an attempt to prevent initial and subsequent fractures. This article reviews currently approved modalities of therapy for the prevention and treatment of postmenopausal osteoporosis.

Osteoporosis is a systemic metabolic bone disease with protean clinical, physical, and socioeconomic implications. Reports of osteoporosis date back to before the Early Bronze Age and indicate that despite an active agrarian lifestyle, the early development of low bone mineral density (BMD) placed women at greater risk for fracture.

According to the World Health Organization (WHO), osteoporosis is now widely recognized as a progressive systemic disease characterized by low BMD and microarchitectural deterioration in bone that predisposes patients to increased bone fragility and fracture. Results from the National Osteoporosis Risk Assessment (NORA) study of more than 200,000 healthy postmenopausal women revealed an unexpectedly high prevalence of osteopenia and osteoporosis, resulting in increased risk for fracture.

The importance of screening at risk, early detection of bone loss in accordance with WHO standards, and the implementation of therapy in accordance with National Osteoporosis Foundation (NOF) guidelines is necessary to prevent further bone loss and increased bone fragility and fracture. Multiple modes of therapy should be incorporated into the management of patients with postmenopausal osteoporosis. Before initiation of therapy, however, the risk factors associated with postmenopausal osteoporosis must be identified and assessed (Figure 1).

Postmenopausal women with established risk factors should undergo an evaluation for osteoporosis that includes a comprehensive medical and family history and physical examination, including vital signs and height assessment. Routine laboratory testing should be done and should include:
- a complete blood cell count;
- a serum chemistry panel, including calcium, phosphate, liver-associated enzyme, total alkaline phosphatase, creatinine, and electrolyte levels;
- thyroid function testing; and
- urinalysis.

All postmenopausal women should be considered for BMD testing, particularly all women older than 65 years, regardless of risk factors, and all postmenopausal women 65 years old or younger who have one or more risk factors for osteoporosis other than menopause (Figure 2). Bone mineral density should be measured by dual-energy x-ray absorptiometry (DXA) to evaluate the lumbar spine, femoral neck, and total femur. The diagnosis of osteopenia or osteoporosis based on a T-score should be established before initiation of therapy.

The T-score represents the number of SDs above or below the mean BMD for the young, healthy female population. It is most frequently used for diagnosis of osteoporosis, determination of fracture risk, and assessment of efficacy in clinical trials. Advancing age and low BMD are strongly associated with increased risk of fracture. According to the WHO Task Force, osteoporosis is defined by a T-score of less than −2.5 SD in women without fragility fractures. For each 1 SD decrease in BMD, there is an approximate doubling of fracture risk. After the baseline establishment of metabolic bone disease, subsequent annual clinical evaluations and repeated assessment of BMD should assist in the ongoing management of osteoporosis in postmenopausal women.

Management
The treatment of patients with postmenopausal osteoporosis incorporates...
multiple modes of both pharmacologic and nonpharmacologic therapy. Particularly successful nonpharmacologic management is a program that includes comprehensive patient education. On being informed of a diagnosis of osteoporosis, patients often are uncertain of the short- and long-term prognosis and implications of this condition. In addition to patient information booklets, data provided by the NOF (http://www.nof.org) and the National Institutes of Health (http://www.nih.gov) and their additional links may facilitate compliance with therapy and empower patients to participate in their care.

Additional nonpharmacologic modes of therapy include:

- nutritional supplementations rich in calcium carbonate or calcium citrate;
- supplemental vitamin D;
- exercise, especially weight-bearing and weight-training exercise to maintain current bone mass; and
- avoidance of tobacco, ethanol, caffeine, and high-protein foods.

The NOF has introduced guidelines for the initiation of treatment for patients with postmenopausal osteoporosis (Figure 3).

### Calcium and Vitamin D

Vitamin D supplementation alone does not prevent osteoporosis in healthy postmenopausal women, as indicated by the results of a 2-year randomized, double-blind trial involving 79 monozygotic pairs of twins between the ages of 47 and 70 years with similar baseline characteristics. Scientists concluded that no significant differences occurred in BMD, serum measurements of 1,25-dihydroxyvitamin D, or bone markers, with the exception that the treatment group had increased levels of serum 1,25-dihydroxyvitamin D.

The preventive effects of calcitriol, a synthetic vitamin D analog, in osteoporosis remain unconfirmed; data for calcitriol in osteoporosis in postmenopausal women are limited. In a 2-year double-blind study, 41 men with previously diagnosed primary osteoporosis were randomly assigned to receive calcitriol, 0.25 μg twice daily, or calcium, 500 mg twice daily. The study subjects had no variations in baseline characteristics.

Femoral neck and vertebral BMD remained unchanged after 2 years in both groups. Both groups had a statistically significant reduction (30%; P<.05) in osteocalcin. Only the group treated with calcium had a 30% decline in the bone resorption marker urine N-telopeptide cross-links. The incidence of vertebral fracture was similar in both groups during the 2-year study period. Current NOF recommendations include the concomitant use of calcium carbonate or calcium citrate in daily dosages of 1000 mg to 1500 mg in combination with 400 IU to 800 IU of vitamin D.

### Pharmacologic Management

Initiation of pharmacologic therapy for osteoporosis should begin with a long-term management strategy. Selection of a particular therapeutic agent for the management of osteoporosis is patient-dependent, and the decision for a particular intervention should derive from an evidence-based approach (Table).

### Estrogen and the Women’s Health Initiative

Hormone therapy is an area of ongoing debate in women’s health. Hormone replacement therapy (HRT) is generally accepted as effective in primary prevention of fractures in postmenopausal women. The Women’s Health Initiative (WHI) is a large, complex clinical investigation of a variety of prevention strategies for many of the most common causes of morbidity and mortality among postmenopausal women, including cancer, cardiovascular disease, and osteoporosis-related fractures. The WHI was...
initiated in 1992 with a planned completion date of 2007. Postmenopausal women between the ages of 50 and 79 years were enrolled into either a clinical trial (N = 64,500) or an observational study (N = 100,000).10

The clinical trial component of the WHI is a randomized, comparative trial that includes the following overlapping components:
- sustained low-fat diet versus self-selected dietary modification;
- HRT (conjugated equine estrogens [CEE], 0.625 mg/d, plus medroxyprogesterone acetate [MPA], 2.5 mg/d, [CEE plus MPA] or estrogen therapy [CEE, 0.625 mg/d alone] versus placebo; and
- calcium plus vitamin D supplementation versus placebo.

The overall benefit versus risk assessment is a central focus in each of the clinical trial components. The HRT component of the WHI was halted early because of health risks that exceeded health benefits during an average follow-up of 5.2 years.10,11

The HRT component of the WHI was designed as a randomized, controlled primary prevention trial with a planned duration of 8.5 years.11 This component included 16,608 postmenopausal women between the ages of 50 and 79 years with an intact uterus at baseline; 8506 received CEE plus MPA, and 8102 received a placebo. The primary outcome was coronary heart disease (CHD), which included nonfatal myocardial infarction and CHD-related death. Invasive breast cancer was the primary adverse outcome. A global index was defined as the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

The safety monitoring board recommende/d stopping the trial of CEE plus MPA versus placebo because the test statistic for breast cancer exceeded the stopping boundary for this adverse effect, and this adverse effect and the global index statistic supported risks exceeding benefits.10,11

There is no Food and Drug Administration (FDA)–approved indication for CEE and the combination of CEE plus MPA to reduce either vertebral or hip fractures.

Importantly, postmenopausal women who decide to discontinue HRT must be assessed for risk of fracture. Results of the NORA trial suggest that women who recently stopped using HRT had an approximately 50% greater risk of bone fracture than women who never used HRT.4,10,11

**Calcitonin-Salmon Nasal Spray**
Calcitonin-salmon nasal spray is well tolerated and reduces risk of vertebral fracture in postmenopausal women with osteoporosis. The Prevent Recurrence of Osteoporotic Fracture (PROOF) study12 was a 5-year, double-blind trial involving 1255 postmenopausal women who were randomly assigned to receive 100 IU, 200 IU, or 400 IU of calcitonin-salmon nasal spray or placebo daily along with 1000 mg of calcium and 400 IU of vitamin D per day. Baseline characteristics (ie, age, years since menopause, body mass index, lumbar spine BMD, and calcium intake) were similar in all groups. Follow-up was obtained at 1, 3, 6, 9, and 12 months and every 6 months thereafter. Intention-to-treatment was used for incident vertebral fracture endpoint with at least one follow-up radiograph.

All groups had between a 1% and a 1.5% increase in BMD in the lumbar spine. Compared with patients receiving placebo, patients who received the 200-IU daily dose had a 33% reduction in risk of new vertebral fracture. The group receiving 100 IU/d and the group receiving 400 IU/d did not demonstrate statistical significance when compared with the group receiving placebo, and no significant difference in the risk of nonvertebral fracture was found between the group receiving placebo and the group receiving calcitonin-salmon nasal spray. Overall, calcitonin-salmon nasal spray demonstrated improvement in BMD and a reduction in risk of vertebral fractures, but no reduction in hip or nonvertebral fractures.12

**Selective Estrogen Receptor Modulator Therapy**
Raloxifene hydrochloride, a selective estrogen receptor modulator (SERM), is indicated for the prevention and treatment of osteoporosis in postmenopausal women. The effect of raloxifene on the incidence of fracture and BMD was examined in the Multiple Outcomes of Raloxifene Evaluation (MORE), a randomized, double-blind study.13 This study evaluated 7705 women with osteoporosis who had been postmenopausal for at least 2 years. The primary endpoints of the study were the effects of raloxifene on incident vertebral fractures and BMD. The secondary endpoint was any incident nonvertebral fracture.

Results of the MORE study demonstrate that at 3 years, raloxifene increases lumbar spine and femoral neck BMD by 2.6% and 2.1%, respectively. In a subgroup analysis of women with no prior vertebral fracture, raloxifene reduced vertebral fractures by 55% compared with placebo. In patients with prior vertebral fracture,
raloxifene reduced vertebral fractures by 30% compared with placebo. The MORE investigators observed no significant reduction in hip fractures.13

Bisphosphonates
Bisphosphonates are considered the mainstay of current medical management of postmenopausal osteoporosis. This class of therapeutic agents contains the chemical structures of two phosphate groups attached to a single carbon atom, thereby facilitating a high affinity for bone through binding to the hydroxypatite in bone. These agents inhibit bone resorption by cellular effects on osteoclasts. Bisphosphonates remain in bone for long periods after absorption and are eliminated primarily through the urine. Although a number of parenteral bisphosphonates are available, current clinical practice guidelines include the use of enteral bisphosphonates, including alendronate sodium and risedronate sodium, both of which are approved by the FDA for the prevention and treatment of osteoporosis.

Alendronate significantly increases BMD and helps to prevent vertebral and nonvertebral fractures in postmenopausal women. The Fracture Intervention Trial, a double-blind study, involved 6459 postmenopausal women. This study was subdivided into two arms, the vertebral fracture arm (VFA)14 and the clinical fracture arm (CFA).15 In both arms, women were randomly assigned to groups that received either placebo or alendronate sodium, 5 mg/d for the first 2 years and 10 mg/d for the remainder of the trial.

In the VFA,14 2027 women with preexisting vertebral fractures were studied for 3 years. In the VFA, the risk of radiographically documented vertebral fracture was 47% lower in the alendronate-treated group compared with that in the group receiving placebo. In the CFA,15 4432 women without preexisting vertebral fracture and femoral neck BMD T-score of less than or equal to 1.6 at baseline were studied for 4 years. In this study, 5.8% of patients in the placebo arm had at least one vertebral fracture, compared with 2.9% of patients in the alendronate arm. Overall, alendronate demonstrated a reduction in the incidence of vertebral fractures. Alendronate reduced the incidence of osteoporotic hip fractures in patients with and without a history of vertebral fracture.14 Alendronate sodium is currently available in a daily (5 mg, 10 mg) and a once-weekly (35 mg) dose.

Risedronate is another FDA-approved bisphosphonate for the prevention and treatment of postmenopausal osteoporosis; it is available in a daily (5 mg) and a once-weekly dose (35 mg).

The Vertebral Efficacy with Risedronate Therapy (VERT) trial was a randomized, double-blind 3-year study conducted at multiple centers in North America, Europe, and Australia.16

The North American arm of the VERT trial enrolled 2458 women who were at least 5 years postmenopausal with at least two radiographically identified vertebral fractures or one vertebral fracture and low lumbar BMD, defined as a T-score of less than or equal to 22.0. The multinational arm of the VERT trial17 enrolled 1226 women who were at least 5 years postmenopausal with at least two radiographically confirmed vertebral fractures.

In both studies, women were randomly assigned to receive risedronate sodium, 2.5 mg/d; risedronate sodium, 5 mg/d; or placebo. The primary endpoint was vertebral fracture incidence over 3 years. Other efficacy measures included radiographically confirmed nonvertebral osteoporosis-related fractures.16,17

In the North American arm of the VERT trial,16 risedronate reduced the incidence of vertebral fracture by 41%. In the multinational arm of the VERT trial,17 risedronate reduced the incidence of vertebral fracture by 49%. These findings demonstrate that risedronate reduces the incidence of vertebral fracture in postmenopausal women.

The Risedronate Hip Intervention Program (HIP) study19 enrolled two groups of women to assess the effect of risedronate on hip fractures in women with osteoporosis. One group consisted of women with osteoporosis (defined as femoral neck BMD T-score ≤ −4.0 or BMD T-score ≤ −3.0, with at least one risk factor for hip fracture) between the ages of 70 and 79 years. The other group consisted of women 80 years of age and older who had at least one nonskeletal risk factor for fracture. Bone mineral density was not a required criterion in this group. Baseline vertebral fractures were present in 39% of the 5445 patients in the younger age group and 45% of the 3886 patients in the older age group. The primary endpoint was the occurrence of hip fracture.

Findings from the HIP study18 indicate that treatment with risedronate for 3 years decreased the incidence of hip fracture by 40% in the younger group of patients, compared with the older patient population. In women aged 80 years and older, there was no significant reduction in the incidence of hip fracture. Risedronate is indicated to reduce the incidence of a composite endpoint of vertebral and nonvertebral osteoporosis-related fractures.

Pamidronate disodium and ibandronate sodium, parenteral bisphosphonates administered every 3 months, offer yet another option; however, parenteral bisphosphonate therapy should be reserved for special clinical circumstances until its efficacy in the prevention of fractures and its long-term safety have been established.19

Anabolic Agents
Parathyroid hormone (PTH) stimulates bone production and improves bone mass in postmenopausal women. Teriparatide, a synthetic form of PTH, is indicated for the treatment of patients with postmenopausal osteoporosis at high risk for fracture. Once-daily injections of PTH or its amino-terminal fragments increase bone formation and bone mass without causing hypercalcemia, but their effects on fractures are unknown.20

In a placebo-controlled study, 1637 postmenopausal women with prior vertebral fracture were randomly assigned to groups that received 20 μg of PTH (1-34), 40 μg of PTH (1-34), or placebo, administered subcutaneously by the women daily.20 Results of this study demonstrate that treatment of postmenopausal osteoporosis with PTH (1-34) decreases the risk of vertebral and nonvertebral fractures; increases vertebral, femoral, and total body BMD; and is well tolerated.

Teriparatide should be administered as a subcutaneous injection. The recommended dose is 20 μg/d. The prescribing information for teriparatide includes a
black box warning because osteosarcoma occurred in both male and female rats during initial investigational studies. Substantial differences distinguish rat and human bone biology and responses to teriparatide; to date, no cases of osteosarcoma have been reported in humans treated with teriparatide.20

Vertebroplasty and Kyphoplasty

Patients who undergo vertebroplasty or kyphoplasty have a substantial decrease in pain and significant increase in mobility.21 Kyphoplasty, a new technique for treating vertebral compression fractures, is a safe, effective procedure for restoring vertebral height, reducing pain, and improving overall function in patients with osteoporotic fractures. Kyphoplasty involves placement of inflatable bone tamp into the vertebral body followed by administration of bone cement, resulting in increased vertebral body height. In one study, kyphosis improved by more than 50%, and height of fractured vertebrae was increased if the procedure was performed within 3 months of the occurrence of fracture.22 In another study, 70 kyphoplasty procedures were performed in 30 patients with primary or secondary osteoporosis-related vertebral compression fractures.22 The procedures restored nearly half of the lost height in 70% of patients with no major complications.23 Kyphoplasty is a preferred adjunctive treatment in the management of postmenopausal osteoporosis after a vertebral compression fracture.

Investigational Modes of Therapy

In the past several years, researchers have determined that the chief intercellular signaling pathway that dictates bone remodeling is mediated by at least three members of the tumor necrosis factor (TNF) and the TNF receptor (TNFR) superfamily, including the following:
- the receptor activator of nuclear factor-κB (RANK), which is a receptor on the preosteoclast and mature osteoclast;
- a hormone-like molecule called κB RANK ligand (RANKL), which is produced by the osteoblast or stromal cell and which stimulates osteoclast formation and activation of mature osteoclasts to resorb bone; and
- a natural, soluble decoy receptor called osteoprotegerin (OPG), which downregulates the resorptive process by competing with RANK for RANKL.

Ongoing investigational research has evaluated the biology of the OPG/RANK/RANKL signaling system and opportunities for therapeutic intervention. In the future, a fully human monoclonal antibody to OPG that inhibits bone resorption may have clinical utility.23,24

Comment

Bisphosphonates are generally considered the drugs of choice for most patients with osteoporosis. This preference prevails especially for older patients at high risk for hip fracture, as both alendronate and risedronate have been found to be protective against hip fracture. Although parenteral forms of bisphosphonates are available, the once-weekly administration of the enteral form is preferred and facilitates patient compliance. Among younger women, in whom hip fracture is less common, the SERM raloxifene may be a good option.

New anabolic modes of therapy (ie, PTH) appear promising for the management of severe osteoporosis. Available data suggest that PTH can dramatically increase BMD; however, only short-term data are currently available. Over time, greater risk reduction with PTH may be demonstrated. At this time, however, no data are available suggesting that protection against fractures is better with PTH than with bisphosphonates.

In the future, other therapeutic classes will be introduced that may dramatically change the manner in which patients with postmenopausal osteoporosis are evaluated and treated.

References

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