Hormone therapy was long considered the best medical therapy for osteoporosis. If it is prescribed for bone health, however, it is no longer the drug of choice in view of its side effect profile. This loss leaves a tremendous therapeutic gap. Indeed, osteoporosis is a large and growing problem in the United States. Approximately 10 million American women have osteoporosis; it has been diagnosed in only 29%, and only 14% of women with diagnosed osteoporosis are receiving therapy.1 With life span increasing, a woman today can expect to live to the age of 85 years, living one third of her life in the postmenopausal period, and thus subject to diseases associated with estrogen deficiency, such as osteoporosis.2

Osteoporosis leaves bones fragile and prone to fracture. Fractures, particularly certain types of fractures, are associated with significant morbidity and mortality in elderly patients. After a hip fracture, for instance, 24% of patients die within 1 year,3 50% will be permanently incapacitated,4 and 20% will require long-term nursing home care.5 Vertebral fractures are equally devastating, leading to acute and chronic back pain, lung disease, gastrointestinal problems, depression, and a 5% to 10% increase in mortality. Preventing osteoporosis is a lifelong goal. Teenagers should be educated on how to achieve adequate peak bone mass; adults, on how to maintain that bone mass; and seniors, on how to slow bone loss and reduce the risk of falls. Patients also need to understand the appropriate use of supplements, particularly calcium and vitamin D, and agents available for the prevention and treatment of osteoporosis, especially in light of recent findings of the Women’s Health Initiative (WHI) hormone replacement trial.6

Definition of osteoporosis
Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and deterioration of bone tissue, with consequent increase in bone fragility and susceptibility to fracture.4 A unit of measure called the T score was developed by the World Health Organization to compare a patient’s bone mass with the mean value for young, healthy individuals, expressed as a standard deviation score. A T score of -2.5 or lower is consistent with a diagnosis of osteoporosis.

Preventive approaches to the postmenopausal patient
Reducing the risk of falls for at-risk patients is critical. Intrinsic risk factors associated with an increased risk of hip fracture are included in Figure 1. Age is progressively associated with increased risk of falls.7

Calcium
Calcium is a critical part of any prevention program, both for women and men. Recommended daily calcium intake changes during a patient’s lifetime. It is actually highest during the adolescent years, when young people are building toward peak bone mass (Figure 2).8 For those who do not have adequate calcium in their diet,
supplements are necessary, and physicians should educate patients with regard to the nuances of calcium pills. Supplements come in two general types:

- Calcium carbonate: cost-effective, higher percentage of calcium per tablet, should be taken with food, may cause constipation and gas.
- Calcium citrate: lower percentage of calcium per tablet, easily absorbed, taken without regard to food.

Key to the absorption of calcium is vitamin D. Natural sources of vitamin D include liver, cod liver oil, egg yolks, fortified milk, and sunshine. For the majority of people who do not find sufficient vitamin D in their diet, supplements should be recommended (400 IU for adults, 800 IU for seniors).

**Bone mineral density testing**
Testing for bone mineral density (BMD) is important to any assessment of patients at risk for osteoporosis. In fact, in September 2002, the National Osteoporosis Foundation (NOF) applauded the US Preventive Services Task Force recommendation that all women aged 65 years and older be screened for osteoporosis. The NOF recommends BMD testing for all women older than 65 years, regardless of other risk factors. The NOF also recommends testing for:
- postmenopausal women younger than 65 years with one or more additional risk factors for osteoporosis (besides menopause);
- postmenopausal women who have had one or more fractures;
- women who have received hormone replacement therapy for a prolonged period; and
- women considering therapy for osteoporosis and for whom BMD test results influence this decision.

It is also important to test for BMD in patients starting long-term corticosteroid therapy, defined as greater than 7.5 mg of steroids daily for more than 6 months.

**Management of osteoporosis**
The management of osteoporosis has been dynamic during the past few years. Several classes of agents are available for the prevention or treatment of osteoporosis, including hormone therapy, calcitonin, bisphosphonates, and selective estrogen receptor modulators (SERMs). Until recently, hormone therapy was the mainstay of preventive treatment. The WHI hormone replacement trial showed a decreased risk of hip fractures with estrogen plus progestin treatment. However, since the cessation of the WHI estrogen plus progestin study, recommendations for the use of hormone therapy suggest consideration of alternative treatment modalities for osteoporosis. Indeed, the label changes on estrogen plus progestin formulations confirm this statement.

**Calcitonin**
Calcitonin is approved for the treatment (ie, reduction in fracture risk), but not prevention (increasing bone density) of osteoporosis. Although calcitonin has been available since 1984, it was not widely used because of its high cost and
Maby • Prevention and treatment of osteoporosis

Bisphosphonates
Bisphosphonates, as a class, are currently the most potent antiresorptive agents available. Although many bisphosphonates are on the market today, comments here are limited to the two that are approved by the FDA for the prevention and treatment of osteoporosis: alendronate sodium and risedronate sodium. Both medications are available in oncedaily and once-weekly formulations. Each has a role in reducing hip fracture in selected patients. The once-weekly dosing has been shown to increase bone density, yet no clinical trials have yet been conducted to show a decrease in hip fracture, though it is anticipated that bisphosphonates will have such an effect. Finally, both agents have gastrointestinal side effects and dosing requirements, which consist of taking the tablets on an empty stomach with water only.

To date, eight trials have been conducted with bisphosphonates; only two—the Fracture Intervention Trial (FIT II)12 and the Risedronate Hip Study13—will be discussed here. The FIT II trial examined the effect of alendronate on reduction of hip fractures as a secondary outcome. (The primary outcomes included risk of radiographically evident vertebral fractures, which decreased by 44% overall with alendronate treatment.) In women with femoral neck T scores of less than −2.5, alendronate significantly reduced the risk of hip fracture by 56%.12 However, this effect was not seen in women with osteopenia (T score between −1.0 and −2.5).

More than 9000 women aged 70 years and older were enrolled in the risedronate hip fracture study, the first study to look at hip fracture as the primary end point.13 Patients were enrolled in two groups: those aged 70 to 79 years with low bone density (group 1), and those older than 80 years with more than one risk factor for fracture (group 2). McClung et al13 reported that risedronate significantly reduced the risk of hip fracture for patients in group 1, but not for those in group 2 (Table). In group 1, the risk reduction was limited to patients who had a previous vertebral fracture; other patients had no significant reduction.

These findings raise several key points. First, a previous fracture predicts a second fracture. Women who have suffered any kind of postmenopausal fracture—hip, forearm, vertebrae—are more likely to have a subsequent fracture. And, according to this clinical study, risedronate will help to prevent a second fracture. Second, and perhaps more important, medication alone is not sufficient therapy for women who are at risk of fracture based on clinical signs when bone density is unknown.

### Selective estrogen receptor modulators
The last class of antiresorptive agents are the SERMs, which are not estrogens; they act as estrogen receptor agonists in some tissues (bone and heart) and antagonists in other tissues (breast and uterus). Raloxifene hydrochloride is a SERM that currently is approved both for the prevention and treatment of osteoporosis. Intriguing recent data also suggest that raloxifene may reduce the risk of breast cancer,14 as well as cardiovascular events in high-risk women,15 as opposed to estrogen plus progestin, which appears to increase the risks for breast cancer and cardiovascular events. Like hormone therapy, however, raloxifene does appear to increase the incidence of venous thromboembolism. Some women also have reported increased incidence of hot flashes.

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial examined the use of raloxifene in postmenopausal women.16 Compared with placebo, raloxifene significantly increased BMD in both the spine and the femoral neck. Furthermore, raloxifene decreased the risk of vertebral fracture both in women with and without prevalent fractures. In women with a previous fracture, the rel-

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| Effect of Risedronate Sodium on Incidence of Hip Fracture in Elderly Women* |
|-------------------------------|-----------------|
| Group | Incidence of hip fracture, % |
|       | Risedronate | Placebo | P value |
| Group 1 (aged 70 to 79 years with low bone density†) | | |
| Overall | 1.9 | 3.2 | .009 |
| With vertebral fracture | 2.3 | 5.7 | .003 |
| No vertebral fractures at baseline | 1.0 | 1.6 | .14 |
| Group 2 (aged 80 years and older with more than one risk factor for fracture) | 4.2 | 5.1 | .35 |

†All patients assigned to risedronate: relative risk, 0.70; 95% confidence interval, 0.6 to 0.9; P = .02
‡Hip T score = −4.
ative risk reduction was 0.66 (95% confidence interval [CI] = 0.55 to 0.81). In women without a prevalent fracture the relative risk reduction was 0.51 (95% CI = 0.35 to 0.73). The MORE trial also reported an impressive finding, though it was not a primary outcome of the study: there was a 72% reduction in the risk of invasive breast cancer in women receiving raloxifene for 4 years ($P>0.001$).14

**Future trends**

Although a number of options are available to replace hormones in the prevention and treatment of osteoporosis, many more agents are currently under investigation and in development. These possibilities include long-acting bisphosphonates and new SERMs, as well as parathyroid hormone, statins, and even soy. Agents that are currently available act only by decreasing bone resorption. The eventual goal, however, is not only to prevent bone loss, but also to enhance bone formation.

**Comment**

Until this year, hormone therapy was largely regarded as being safe for short- and long-term use, suitable for a range of maladies from hot flashes to osteoporosis. Cessation of the estrogen plus progesteron arm of the WHI hormone replacement trial and the confirmed association with cardiovascular events and breast cancer radically change this concept of hormone use. It is now recommended that the estrogen plus progesterin combination not be used for the prevention of cardiovascular disease or osteoporosis, but only for the short-term amelioration of symptoms associated with menopause.

A number of nonhormonal products are available for the treatment of osteoporosis, including calcitonin, bisphosphonates, and SERMs. Certain of these, such as the SERM raloxifene, have shown other benefits as well: raloxifene appears to reduce the risk of invasive breast cancer and cardiovascular disease (among high-risk patients). At least, it appears that these agents do not suffer from the significant drawbacks associated with hormone therapy and may fill the gap in the management of osteoporosis left by the elimination of hormone therapy.

**Addendum**

In December 2002, the FDA approved a new medication for the treatment of osteoporosis. This new agent, teriparatide, or parathyroid hormone, shows great promise in reversing bone loss. Previously, all modes of therapy for osteoporosis were inhibitors of bone resorption. Teriparatide is the first agent available to directly stimulate bone formation by increasing the number and action of osteoblasts. In the clinical trials on which the FDA based its approval, men and women with osteoporosis treated with teriparatide, calcium, and vitamin D had a significant increase in bone density of the hip and spine. The data demonstrated that teriparatide reduced the relative risk of spine fractures by 65% and lowered risk of nonspinal fractures by 53% compared with placebo. Teriparatide represents an important new advance in the therapy for osteoporosis.

**References**


