Osteoporosis: Part II. Nonpharmacologic and Pharmacologic Treatment

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Family physicians will frequently encounter patients with osteoporosis, a condition that is often asymptomatic until a fracture occurs. Treatment of the fracture can be initiated without further diagnostic testing. Thereafter, treatment of osteoporosis includes (1) prevention of further bone loss through weight-bearing exercise, tobacco and alcohol avoidance, hormone replacement therapy in women, and raloxifene and calcium supplementation; (2) treatment of fracture-related pain with analgesics and calcitonin; (3) building bone mass when feasible with alendronate; and (4) modifying behaviors that increase the risk of falls. Patients without fracture who are at risk for osteoporosis can also benefit from these preventive measures. Furthermore, women of all ages should be encouraged to maintain a daily calcium intake of 1,000 to 1,500 mg and to participate in weight-bearing exercise for 30 minutes three times weekly to reduce their risk of falls and fractures. Persons at risk should avoid medications known to compromise bone density, such as glucocorticoids, thyroid hormones and chronic heparin therapy. (Am Fam Physician 2001;63:1121-8.)

Members of various family practice departments develop articles for "Problem-Oriented Diagnosis." This article is one in a series coordinated by the Department of Family Medicine at the Uniformed Services University of the Health Sciences, Bethesda, Md. Guest editors of the series are Francis G. O'Connor, LTC, MC, USA, and Jeannette E. South-Paul, COL, MC, USA.

This is part II of a two-part article on osteoporosis. Part I, "Evaluation and Assessment," appeared in the previous issue (Am Fam Physician 2000;63:897-904,908).

To prevent the problem of osteoporosis-related fractures, family physicians and other primary health care professionals should emphasize prevention in younger patients and select appropriate therapies for use in those who are already affected.

The approach to the patient is governed by the presentation. The greatest challenge for clinicians is to know which asymptomatic patients would benefit from screening for osteoporosis, rather than merely to determine a treatment regimen for those with known disease. All women and girls should be counseled concerning calcium intake and physical activity. Assessment of osteoporosis risk is also important when following a patient for a chronic disease known to cause secondary osteoporosis. Preventive measures are always the first step in therapy.

If the physician suspects osteoporosis in a man or finds evidence of a pathologic fracture in a man or a woman, the next steps are to assess the patient's risk by taking a medical history and to determine bone mineral density (BMD). BMD measurement and laboratory evaluation are necessary to document the extent of bone loss and rule out secondary causes of osteoporosis. If there is clinical evidence of a particular condition, the focus of the evaluation can shift to the suspected condition once the basic laboratory study has been completed.

Behavior Modification

Patients requesting risk assessment for osteoporosis may require only a history and physical examination, and the provision of patient information. Patients at risk for osteoporosis should be counseled about behavioral measures that can decrease their risk of bone loss. Tobacco use and excessive consumption of alcohol and caffeine should be discouraged.[1] A balanced diet with adequate calcium and vitamin D intake and a regular exercise program (see below) should be encouraged to retard bone loss. The use of medications (e.g., glucocorticoids) that decrease bone mass should be avoided, if possible. The importance of maintaining estrogen levels in women should be emphasized. Measurement of bone density should be considered in patients who present with risk factors but need "proof" before agreeing to take preventive measures.

Exercise

More than 20 randomized, controlled trials[2] suggest that regular physical exercise can

All women and girls should be counseled about calcium intake and physical activity, and their relation to osteoporosis.

reduce the risk of osteoporosis and delay the physiologic decrease of BMD. Short-term and long-term (measured up to 12 months) exercise training such as walking, jogging and stair climbing in healthy, sedentary postmenopausal women resulted in improved bone mineral content.[3] Bone mineral content increased more than 5 percent above baseline after short-term weight-bearing exercise training. With reduced weight-bearing exercise, bone mass soon reverted to baseline levels.[4,5] Similar increases in BMD have been found in women who participate in strength training.[6] In the elderly, progressive strength training has been demonstrated to be a safe and effective form of exercise that reduces risk factors for falling and may also enhance BMD.[7]

Athletes who exercise regularly usually have above-average bone mass. However, the positive effect of exercise on the bones of young women is dependent on normal levels of endogenous estrogen. The low estrogen state of exercise-induced amenorrhea outweighs the positive effects of exercise and results in diminished bone density. When mechanical stress or gravitational force on the skeleton is removed (e.g., bed rest, immobilization of limbs or paralysis), bone loss is rapid and extensive.[8]

Estrogen deficiency results in diminished bone density in women. Weight-bearing exercise can significantly increase the BMD of menopausal women.[5] Furthermore, weight-bearing exercise and estrogen replacement therapy (ERT) have independent and additive effects on the BMD of the limbs, spine and Ward's triangle (hip).

No randomized, prospective studies have systematically compared the effect of various activities on bone mass. Recommended activities include walking and jogging, weight training, aerobics, stair climbing, field sports, racquet sports, court sports and dancing. Swimming is of questionable value in terms of bone density (because it is not a weight-bearing activity), and there are no data on cycling, skating or skiing. Any increase in physical activity may have a positive effect on bone mass in women who have been sedentary. To be beneficial, the duration of exercise should be between 30 and 60 minutes and the frequency at least three times per week.

Pharmacologic Therapy

ESTROGEN

The decision to intervene with pharmacologic therapy involves clinical judgment based on a global assessment, not just BMD measurement. All therapeutic agents currently approved for the prevention and treatment of osteoporosis work through inhibiting or decreasing bone resorption. Maintaining adequate estrogen levels remains the most important way of maintaining adequate bone density in women.[9,10] All women with decreased bone density should be offered estrogen replacement therapy (ERT) unless contraindications exist. The most common contraindications are listed in *Table 1*.[11] Conjugated estrogens in dosages of 0.625 and 1.25 mg per day and transdermal estrogen (a weekly patch containing 0.05 mg) are equally effective in reducing bone loss in postmenopausal and oophorectomized women.[12]

Studies have been made of the effect of the timing of initiation and the duration of postmenopausal estrogen therapy on BMD.[13,14] Current users who started ERT at menopause had the highest BMD levels, which were significantly higher than "never" users or "past" users who started at menopause and continued it for at least 10 years. BMD was similar in women using unopposed estrogen or estrogen plus progestin, in women younger or older than 75 years and in current smokers or nonsmokers.

Current users who started ERT within five years of menopause had a decreased risk of hip,

wrist and all nonspinal fractures compared with those who never used estrogen. Long-term users who initiated therapy five years after menopause had no significant reduction in risk for all nonspinal fractures, despite an average duration of use of 16 years.[13] Therefore, early initiation of ERT with respect to menopause may be more important than the total duration of use. Estrogen initiated early in menopause and continued into late life appears to be associated with the highest bone density.

As more and more women use ERT, concern has grown regarding its impact on breast cancer risk. The relationship between the use of hormones and the risk of breast cancer in postmenopausal women was assessed in a follow-up survey of participants in the Nurses' Health Study in 1992.[15] The risk of breast cancer was found to be significantly increased among women who were currently using estrogen alone or estrogen plus progestin, compared with postmenopausal women who had never used hormones. The risk of breast cancer in women currently taking hormones was increased by the same proportions if they had used hormones in the past for five to nine years or for 10 or more years.[15] The addition of progestins to estrogen therapy does not reduce the risk of breast cancer among postmenopausal women.

Although regular physical exercise can reduce the risk of osteoporosis, an excessive amount of exercise is actually associated with the disease.

The only randomized trial of estrogen-progesterone therapy describes secondary prevention of coronary heart disease in postmenopausal women (HERS) and included only women with a prior history of cardiovascular disease.[16,17] Women received either estrogen or estrogen and progesterone. There was an excess of coronary heart disease deaths and a threefold excess risk of venous thrombosis during the first year of the trial in women taking estrogen and a small risk of stroke in women taking estrogen and progesterone. Recommendations at the conclusion of the trial included forgoing estrogen and progesterone therapy in women who already have clinical cardiovascular disease (i.e., secondary prevention).

TABLE 1
Contraindications to ERT for Osteoporosis

Absolute contraindications
History of breast cancer
Estrogen-dependent neoplasia
Undiagnosed or abnormal vaginal bleeding
History of or active thromboembolic disorder
Relative contraindications
Migraine
History of thromboembolism
Familial hypertriglyceridemia
Uterine leiomyomas
Uterine cancer
Gall bladder disease
Strong family history of breast cancer
Chronic hepatic dysfunction
Endometriosis

ERT = estrogen replacement therapy.

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CALCIUM AND VITAMIN D

Calcium supplementation results in small beneficial effects on bone mass throughout postmenopausal life and may reduce fracture rates by more than the change in BMD would predict—possibly as much as 50 percent.[18] Postmenopausal women receiving supplemental calcium over a three-year period in a placebo-controlled, randomized clinical trial[19] had stable total body calcium levels and BMD in the lumbar spine, femoral neck and trochanter compared with women in the placebo group.

Vitamin D increases calcium absorption in the gastrointestinal tract, so that more calcium is available in the circulation and subsequently reabsorbed in the renal proximal tubules. Evidence shows there are significant reductions in nonvertebral fracture rates as a result of physiologic replacement of vitamin D in the elderly.[18] Vitamin D supplementation is important in women of all ages who have limited exposure to sunlight.

Dietary calcium augmentation should be recommended to maintain lifetime calcium levels and to prevent early postmenopausal bone loss. Foods that are rich in calcium are listed in *Table 2*.[20] Most adults should ingest 1,000 mg of elemental calcium per day for optimal bone health.[11,21] Teenagers, pregnant or lactating women, women older than 50 years who are taking ERT, and everyone older than 65 years should ingest 1,500 mg of elemental calcium per day for optimal bone health. If this cannot be achieved by diet alone, calcium supplementation is recommended. Calcium preparations should be compared relative to elemental calcium content. Therefore, it is important that the physician pay attention to the particular form of calcium supplement the patient is taking.

TABLE 2
Calcium-Rich Foods*

Milk (skim, low-fat or whole), 8 oz
Plain yogurt, 8 oz
Frozen yogurt with fruit, 8 oz
Ricotta cheese, part-skim, 4 oz
Sardines, canned, 3 oz
Cooked greens (collards or mustard), 8 oz
Firm cheeses (swiss, edam, brick, cheddar, gouda, colby, mozzarella), 1 oz
Calcium-fortified orange juice, 8 oz

**—Approximately 300 mg per amount listed.*

Adapted with permission from Tresolini CP, Gold DT, Lee LS, eds. Working with patients to prevent, treat and manage osteoporosis: a curriculum guide for health professions. 2d ed. San Francisco: National Fund for Medical Education, 1998.

CALCITONIN

Calcitonin (Calcimar), a hormone directly inhibiting osteoclastic bone resorption, is an alternative for use in patients with established osteoporosis who cannot, will not or should not proceed with ERT.[21] A unique characteristic of calcitonin is that it produces an analgesic effect with respect to bone pain and, thus, is often prescribed for patients who have had an acute osteoporotic fracture. Calcitonin decreases further bone loss at vertebral and femoral sites in patients with documented osteoporosis but has a questionable effect on fracture frequency. Calcitonin has been shown to prevent trabecular bone loss during the first few years of menopause, but it is unclear whether it has any impact on cortical bone.[18] Calcitonin is also thought to be effective in decreasing the fracture rate of vertebrae and peripheral bones.[22]

For reasons that are poorly understood, the increase in BMD associated with calcitonin administration may be transient or resistance may develop. Calcitonin can be provided in two forms, as a nasal inhaler and as an injection. Nasal congestion and rhinitis are the most significant side effects of the nasal form. The injectable formulation has gastrointestinal side effects and is less convenient to use than the nasal preparation. The increase in bone density resulting from this therapy is significantly less than that achieved by alendronate (Fosamax) or estrogen, and may be limited to the spine, but it still has value in reducing the risk of fracture.

BISPHOSPHONATES

Bisphosphonates are effective for preventing bone loss associated with estrogen deficiency, glucocorticoid treatment and immobilization.[23] All bisphosphonates act similarly on bone in binding permanently to mineralized bone surfaces and inhibiting osteoclastic

activity. Thus, less bone is degraded during the remodeling cycle.[23,24]

The Fracture Intervention Trial[25] investigated the effect of alendronate on the risk of fractures (inapparent fractures as well as clinically evident fractures) in postmenopausal women with low bone mass. The risk of clinical fracture in those taking alendronate was one half that of women in the placebo group.

Because food and liquids can reduce the absorption of alendronate (Fosamax), it should be taken with a full glass of water 30 minutes before the first meal or beverage of the day. To lessen the chance of esophageal irritation, patients should not lie down for at least 30 minutes after taking the dose. In addition, patients should consider taking supplemental calcium and vitamin D if their dietary intake is inadequate.

Alendronate and ERT are of comparable efficacy in preventing bone loss; alendronate has a demonstrated positive effect on symptomatic and asymptomatic vertebral fracture rate, as well as on the nonvertebral fracture rate (forearm and hip).[18,25] In clinical trials, alendronate was generally well tolerated and caused no significant adverse effects. Alendronate appears to be effective at dosages of 5 mg per day in preventing osteoporosis induced by long-term glucocorticoid therapy. In placebo-controlled studies[26] of men and women (17 to 83 years of age) who were taking glucocorticoids, the bone density of the femoral neck bone, the trochanter and the total body increased significantly in patients treated with alendronate.

Some small studies[27] suggest an additional benefit of adding alendronate to ERT. However, all of the bisphosphonates accumulate in bone over time, and further research is needed to determine their long-term impact, as well as their potential for use in men and premenopausal women.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Raloxifene (Evista) is the first drug from a new class—selective estrogen receptor modulators—to be studied in the treatment of osteoporosis. Its discovery evolved from a rearrangement of the anti-estrogen tamoxifen (Nolvadex). Raloxifene is thought to block estrogen in a similar manner while also binding and stimulating other estrogen tissue receptors. Raloxifene inhibits trabecular and vertebral bone loss by blocking the activity of cytokines, which stimulate bone resorption.

Raloxifene therapy results in decreased serum total and low-density lipoprotein (LDL) cholesterol levels without having any beneficial effects on serum high-density lipoprotein (HDL) cholesterol or triglyceride levels.[28,29] Reported side effects of raloxifene are vaginitis and hot flushes.[30] Investigators in a trial[31] of more than 7,000 postmenopausal osteoporotic women studied over three years showed a decreased breast cancer risk in those who were already at low risk for the disease. Studies of women at higher risk for breast cancer are currently under way.

A summary of overall treatment strategies is presented in *Table 3*,[32] and guidelines for dosing are presented in *Table 4*.

OTHER MODALITIES

Fluoride increases bone formation by stimulating osteoblasts and increasing cancellous bone formation in patients with osteoporosis. However, the bone is formed only in the spine and is irregularly fibrous and woven with lacunae of low mineral density.[33] Cessation of therapy results in rapid loss of much of the bone formed during treatment. The major side effect of fluoride therapy, gastric distress, may be related to the direct effect of hydrofluoric acid on the gastric mucosa.

Several other drugs have been studied in the treatment of osteoporosis but for various reasons are not accepted therapies. Anabolic steroids produce some increase in bone mass. Despite this benefit, these drugs are seldom used for treating osteoporosis in the United States because of their long-term effects—significant hepatotoxicity, reduced HDL levels and elevated LDL cholesterol levels.[34]

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Evidence from animal studies suggests a beneficial effect of phytoestrogens on bone, but long-term human studies are lacking.[35] Epidemiologic evidence of Asian women having a lower fracture rate than white women, even though the bone density of Asian women is less than that of black women, promotes consideration of the impact of nutrition. It is possible that a high dietary soy intake contributes to improved bone quality in Asian women. A comparison study of a soy protein-high isoflavone diet versus a milk protein or a medium isoflavone-soy protein diet demonstrated that those receiving high isoflavone supplementation had a modest increase in trabecular (vertebral) bone, but not in cortical (femoral) bone.[36]

A topical form of natural progesterone derived from diosgenin in soybeans and Mexican wild yam has been promoted as a treatment for osteoporosis, hot flushes and premenstrual syndrome, and as a prophylactic against breast cancer. However, humans cannot convert diosgenin into progesterone, so eating or applying wild yam extract or diosgenin does not result in increased progesterone levels.[37]

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Glucocorticoids are widely used in the treatment of many chronic diseases, particularly asthma, lung disease and inflammatory and rheumatologic disorders, as well as in patients who have undergone organ transplantation. To achieve the best possible outcome for these patients given the potentially

TABLE 3
Treatment Guidelines for Osteoporosis

Overall strategies
Calcium supplements, with or without vitamin D supplements, or calcium-rich diet
Weight-bearing exercise
Avoidance of alcohol, tobacco products, drugs and excessive caffeine
ERT within five years of menopause for 10+ years
Alendronate (Fosamax)
Raloxifene (Evista)
Calcitonin (Calcimar)
Strategies for patients taking glucocorticoids
Lowest dosage of a short-acting glucocorticoid or use of topical preparations whenever possible
Well-balanced diet, with daily intake of 2 to 3 g of sodium
Weight-bearing and isometric exercise to prevent proximal muscle weakness
Calcium intake of 1,500 mg per day and vitamin D intake of 400 to 800 IU per day after hypercalciuria is controlled
ERT in all postmenopausal women and in premenopausal women with low levels of estradiol
Measurement of BMD at baseline and every six to 12 months during the first two years of therapy to assess treatment efficacy
Treatment with calcitonin or bisphosphonate if bone loss occurs during treatment or if ERT is contraindicated

ERT = estrogen replacement therapy; BMD = bone mineral density.

Adapted with permission from Lane NE, Lukert B. The science and therapy of glucocorticoid-induced bone loss. Endocrinol Metab Clin North Am 1998;27:465-83.

TABLE 4
Agents for Treating Osteoporosis

Medication	*Dosage*	*Route*	*Cost**
Estradiol skin patch (Estraderm)	0.05 mg every week	Topical	$26 to 68
Conjugated estrogens	0.625 to 1.25 mg per day	Oral	16 to 23
Elemental calcium	1,000 to 1,500 mg per day	Oral	13 to 20
Calcitonin (Calcimar)	200 IU per day or 50 to 100 IU per day	Intranasal or subcutaneous/ intramuscular	36 to 59
Vitamin D	400 IU per day (800 IU per day in winter in northern latitudes)	Oral	1
Alendronate (Fosamax)	Prevention: 5 mg per day Treatment: 10 mg per day	Oral	61 (5 mg) 61 (10 mg)
Raloxifene (Evista)	60 mg per day	Oral	61

**—Estimated cost to the pharmacist based on average wholesale prices for one month of therapy (rounded to the nearest dollar) in Red book. Montvale, N.J.: Medical Economics Data, 2000. Cost to the patient will be greater, depending on prescription filling fee.*

devastating effects of systemic steroids, therapy to combat their effects on osteoporosis should begin as soon as the steroid therapy is begun. *Table 3*[32] presents specific guidelines for therapy in these patients.

The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Army Medical Department or the Army Service at large.

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