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Osteoporosis develops in older adults when the normal processes of bone formation and resorption become uncoupled or unbalanced, resulting in bone loss. Fractures are the result of decreased bone mass and strength, and, in the case of wrist and hip fractures, they usually involve a fall. Osteoporosis prevention and treatment programs should therefore focus on strategies that minimize bone resorption and maximize bone formation, as well as on strategies that reduce falls. Optimal treatment and prevention of osteoporosis require modification of risk factors, particularly smoking, physical activity, and diet, in addition to pharmacologic intervention. Osteomalacia, a less common disorder, occurs when bone is inadequately mineralized; the result is a syndrome of bone loss accompanied by bone pain, myopathy, fatigue, and fractures.

DEFINITION OF OSTEOPOROSIS

Osteoporosis was defined previously by a consensus panel as a “disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture incidence.” According to this definition, the diagnosis of osteoporosis requires the presence of a fracture. The World Health Organization now defines osteoporosis by bone mineral density (BMD) measurement, which allows diagnosis and treatment of osteoporosis prior to incident fracture. If a woman has BMD measurement at any site < 2.5 standard deviations below the young adult standard (a T score of < -2.5), the diagnosis of osteoporosis can be made. Further, women with osteopenia (low bone mass, with a T score of ≥ -2.5 but < -1) and normal bone mass (with a T score of ≥ -1) can also be identified. Thus, the clinician can make the diagnosis of osteoporosis and begin the appropriate therapy prior to fracture in older adults. In addition, women with osteopenia can be placed on a preventive regimen and then followed carefully for further bone loss. Specific standards for definitions of osteoporosis have not been established for men or for racial and ethnic groups other than white persons, although it appears that similar standards apply to men and to Hispanic women.

THE EPIDEMIOLOGY AND CONSEQUENCES OF OSTEOPOROSIS

In 1990 more than 1.25 million hip fractures were reported worldwide in women, and 500,000 in men. In the United States the estimated numbers of hip and vertebral fractures in women are more than 250,000 and 500,000, respectively, per year. To this number must be added fragility fractures in men, which occur at about one third the rate seen in women. Thus, approximately 1 million Americans suffer fragility fractures each year, at a cost of more than \$14 billion. The consequences of osteoporosis include diminished quality of life, decreased independence, and increased morbidity and mortality. The pain and kyphosis, height loss, and other changes in body habitus that occur as a result of vertebral compression fractures erode quality of life for both women and men. In addition, the functional status of patients who have had vertebral crush fractures may also decrease. These patients may be unable to bathe, dress, or ambulate independently. Increased mortality is related primarily to hip fractures; 20% excess mortality occurs in older persons in the year following hip fracture. In addition, approximately 50% of women do not fully recover prior function after hip fracture. Thus, in older adults, it is important to prevent as many fractures as possible.

REVIEW OF BONE REMODELING

Bone is able to repair itself by actively remodeling, a coupled process (also called *bone turnover*) of bone resorption followed by bone formation; bone remodeling continues throughout life. Local signals, not yet fully understood, bring osteoclasts to specific areas of bone where resorption is initiated and resorption cavities are formed. Once osteoclasts have completed the resorption process, osteoblasts move into the area and begin to lay down osteoid and, later, to calcify the matrix. Under optimal conditions, once bone remodeling is completed in a specific area, the resorption spaces are completely filled with new bone. However, after menopause in women, and with aging in men and women, the remodeling cycle becomes unbalanced, and bone resorption increases more than formation does, resulting in net bone loss. The majority of treatments for osteoporosis act to inhibit bone resorption rather than to increase bone formation.

BONE LOSS

Bone mass changes over the life span of an individual. In women, bone mass increases rapidly from the time of puberty until approximately the mid-20s to mid-30s, at which time peak bone mass is reached. Once women reach peak bone mass, a few years of stability are followed by a slow rate of bone loss, beginning well before the onset of menopause. After menopause, the rate of bone loss is quite rapid—as much as 7% per year—for up to 7 years, as a consequence of estrogen deficiency. In later life bone loss continues, albeit at a slower rate, generally 1% to 2% per year; however, some older women may lose bone density at a higher rate. Data strongly suggest that terminating bone loss at any time will decrease fracture risk. It has been estimated that a 14% increase in bone density in 80-year-old women would halve hip-fracture risk. This 14% increase would also be realized if bone loss were prevented in 70-year-old women. Although studies thus far have focused mostly on women, it is well documented that men lose bone with age. Cross-sectional studies have detected a slower rate of bone loss in men than in women, but, in a longitudinal study, rates of bone loss in men were found to equal those of older women, although men start from a higher bone mass. It is estimated that men aged 30 to 90 years lose approximately 1% per year in the radius and spine; some men with risk factors lose as much as 6% per year. These data suggest that older men lose bone at rates similar to those of older women; however, vertebral fracture rates in men are lower. Both men and women lose predominantly cancellous bone, which is concentrated in the vertebral spine. Cortical bone accounts for 45% to 75% of the mechanical resistance to compression of the vertebral spine, and men actually gain cortical bone through periosteal bone deposition. Men also increase the cross-sectional area of their vertebrae by 15% to 20%, increasing maximum load levels until the age of 75. The increased bone strength seems to be reversed by thinning of the cortical ring by age 75, the age at which men begin to present with vertebral fractures. Although bone loss at the hip has not been extensively studied in men, in cross-sectional analyses healthy men were found to lose 40% of femoral neck BMD between the ages of 20 and 90 years.

PATHOGENESIS OF OSTEOPOROSIS

Estrogen Deficiency in Women

The pathogenesis of osteoporosis in women is complex. Factors that affect the level of peak bone mass, the rate of bone resorption, and the rate of bone formation need to be considered. Peak bone mass appears to be 75% to 80% genetically determined, although which genes are involved is not clear. A number of candidate genes that may be important to osteoporosis are being explored currently: vitamin D receptor, estrogen receptor, transforming growth factor, interleukin-6, interleukin-1 receptor 2, type I collagen genes, and collagenases. Several factors may work to increase bone resorption in older women. After menopause, and with estrogen deficiency, a variety of factors that act locally on bone may lead to increased bone resorption. Factors thought to play a role in the bone loss of estrogen deficiency include interleukin-1, interleukin-1 receptor antagonist, interleukin-6, and tumor necrosis factor, as well as their binding proteins and receptors. (For hormone replacement therapy regimens, see [Table 49.1](#).)

Calcium Deficiency and Secondary Hyperparathyroidism

The mechanism by which older men and women continue to lose bone is likely related to calcium deficiency, which produces secondary hyperparathyroidism. Parathyroid hormone (PTH) is a potent stimulator of bone resorption when chronically elevated. Aging skin and decreased exposure to sunlight reduce the conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D₃) by ultraviolet light, and the

result is vitamin-D insufficiency in older adults. Vitamin-D insufficiency, in turn, reduces the absorption of calcium. Further, older adults tend to ingest inadequate amounts of vitamin D and calcium. As a result of decreased serum levels of calcium, PTH—acting to maintain serum levels of calcium—increases, which leads to increased bone resorption. In one study, older women (mean age 79 years) hospitalized with a hip fracture were found to have lower 25(OH)D levels and higher PTH, higher bone resorption, and lower bone formation than women in the control group (mean age 77 years). Further, data from the Study of Osteoporotic Fractures indicate that women with low fractional absorption of calcium are at increased risk for hip fracture. (See also [Endocrine and Metabolic Disorders](#), for more on disorders of calcium metabolism.)

Androgens in Men

Androgens are important determinants for peak bone mass in men. Bone accretion is closely related to sexual maturity, and men who have abnormal puberty or delayed puberty have reduced bone mass. In addition, men with estrogen deficiency or resistance have decreased bone mass and failure of epiphyseal closure. Several studies have demonstrated that late-onset hypogonadism can also play a role in osteoporosis in men. Although it is evident that severe male hypogonadism can cause osteoporosis, the effect of moderate decreases in testosterone levels in aging men on rates of bone loss is uncertain. One study found that more than 60% of men presenting with hip fracture had low testosterone levels, compared with about 20% of those in the control group.

Changes in Bone Formation

In men and women, osteoblast activity appears to decrease with aging, compounding the bone loss that results from increased resorption seen with aging and, for women, with menopause. Growth factors, such as transforming growth factor B and insulin-like growth factor 1, may be impaired with estrogen deficiency or with aging, resulting in decreased osteoblast function.

DIAGNOSIS OF OSTEOPOROSIS AND PREDICTION OF FRACTURE

Risk Factors

Risk factors for osteoporosis and osteoporotic fracture have been identified and have been used to determine who should be placed on preventive or therapeutic regimens. Risk factors, however, are mediocre predictors of low bone density and fractures, and it is more useful to identify modifiable risk factors and to implement change as part of a treatment or preventive program. [Table 27.1](#) lists modifications of risk factors of osteoporosis; all of these risk factors should be addressed by the clinician as part of the routine care of an older adult. Risk factors can also be used to identify women < 65 years of age who should have BMD screening.

Secondary Causes

The diagnosis of idiopathic or primary osteoporosis is made by bone density measurement prior to fracture or by incident fracture. Exclusion of other diseases that may present as fracture or with low bone mass is important in the evaluation of women and men with osteoporosis, since different treatment would be required. The major secondary causes of osteoporosis are listed in [Table 27.2](#), along with laboratory tests used to exclude each disease. These laboratory tests should be considered for persons who present with acute compression fracture or who present with a diagnosis of osteoporosis by BMD measurement. The most common causes of secondary osteoporosis in women are primary hyperparathyroidism and glucocorticoid use. Men are more likely to have a secondary cause of osteoporosis than women; as many as 50% of osteoporotic men may have a secondary cause. The most commonly reported secondary causes of osteoporosis in men include hypogonadism and malabsorption syndromes, including gastrectomy. Medications that might have a detrimental effect on bone should be given with adjusted doses or discontinued. Medications that have been shown to adversely affect BMD include glucocorticoids, excess thyroid supplement, anticonvulsants, methotrexate, cyclosporine, and heparin. In older adults, glucocorticoids and thyroid hormone are used quite commonly; accordingly, clinicians should consider the effects these medications may have on the already increased risk of fracture when prescribing them for older adults.

Glucocorticoids result in bone loss primarily through the direct suppression of bone formation, although they also further reduce sex hormone levels and cause secondary hyperparathyroidism through their effects on intestinal calcium absorption. The prevalence of vertebral fractures in persons taking glucocorticoids for 1 year is estimated to be 11%. The rate of trabecular bone loss is dose dependent and generally occurs in the first 6 months of therapy. Although inhaled corticosteroids have not been as well studied, high doses of high-potency inhaled steroids may also result in bone loss. The best strategy for older persons who require long-term glucocorticoid therapy is to maximize bone health by a variety of interventions. It is important to use the lowest possible dose of glucocorticoids, to assure adequate calcium and vitamin D intake (see the treatment section, below), and to provide appropriate replacement of sex hormones in men (testosterone) and women (estrogen). Further, alendronate and intermittent etidronate have been shown to successfully prevent bone loss that is due to glucocorticoid therapy when they are initiated at the same time as the steroids (see the treatment section, below).

Bone Density Measurement

BMD, or bone mass measurement, is the best predictor of fracture. In fact, it is a better predictor of fracture than cholesterol level is a predictor of coronary heart disease. The relative risk of fracture is 10 times greater in women in the lowest quartile of BMD than in women whose BMD is in the highest quartile.

Bone density of the hip, spine, wrist, or calcaneus may be measured by a variety of techniques. The preferred method of BMD measurement is dual-energy radiographic absorptiometry. BMD of the hip, anterior-posterior spine, lateral spine, and wrist can be measured with this technology. Whether all women should undergo BMD screening is controversial. The National Osteoporosis Foundation, in conjunction with numerous specialty organizations, recommends BMD testing for all women aged 65 years and over, regardless of risk-factor status. On the other hand, the U.S. Preventive Services Task Force states that there is insufficient evidence to recommend for or against BMD screening. Indications for BMD testing are listed in [Table 27.3](#). The cost for dual-energy radiographic absorptiometry testing is between \$200 and \$300, and Medicare and Medicaid will cover the cost if indications for its use (eg, estrogen deficiency) are met. BMD testing may also be used to establish the diagnosis and severity of osteoporosis in men, and it should be considered for men with low-trauma fracture, radiographic criteria consistent with low bone mass, or diseases known to place a person at risk for osteoporosis. Data relating BMD to fracture risk are derived from studies of women, but data suggest that similar associations may be valid for men.

Biochemical Markers of Bone Turnover

Serum and urine biochemical markers can estimate the rate of bone turnover (remodeling) and may provide additional information to assist the clinician. A number of markers have been developed that reflect collagen breakdown (or bone resorption) and bone formation. Several markers have been associated with increased hip-fracture risk, decreased bone density, and bone loss in older adults. In addition, markers of bone resorption and formation decrease in response to antiresorptive treatment. The use of markers in clinical practice, however, is controversial because of the substantial overlap of marker values in women with high and low bone density or rate of bone loss. Further, few studies have compared the response of a particular marker (or combination of markers) and bone density with therapy in order to determine the magnitude of decrease of a biochemical marker necessary to prevent bone loss or, more importantly, fracture. Two markers of bone resorption, deoxypyridinoline cross-links and cross-linked N-telopeptides of type I collagen, and one formation marker, bone alkaline phosphatase, may be used in clinical practice to provide an early assessment of treatment efficacy. A decrease from baseline levels in the level of these markers after 3 to 6 months of therapy would indicate successful treatment.

PREVENTION AND TREATMENT OF OSTEOPOROSIS

The Role of Exercise

Exercise is an important component of osteoporosis treatment and prevention, although exercise alone is not adequate to prevent the rapid bone loss associated with estrogen deficiency in early menopause. Among exercisers in the Rancho Bernardo cohort, those who reported strenuous or moderate exercise had higher BMD at the hip than did those who reported mild or less-than-mild exercise. Similar associations were seen for lifelong regular exercisers and hip BMD. In a randomized study of women ≥ 10 years postmenopausal, the group receiving calcium supplementation plus exercise had less bone loss at the hip than did those

assigned to calcium alone. Further, the effectiveness of high-intensity strength training in maintaining femoral neck BMD as well as in improving muscle mass, strength, and balance in postmenopausal women has been demonstrated, suggesting that resistance training would be useful to help maintain BMD and to reduce the risk of falls among older adults.

Marked decrease in physical activity or immobilization results in a decline in bone mass; accordingly, it is important to encourage older adults to be as active as possible. Weight-bearing exercise, such as walking, can be recommended for all adults. Older persons should be encouraged to start slowly and gradually increase both the number of days as well as the time spent walking each day. (See [Physical Activity](#).)

Calcium and Vitamin D

Calcium and vitamin D are required for bone health at all ages. In order to maintain a positive calcium balance, the current recommendations for calcium intake for postmenopausal women and men aged 65 years and older is at least 1200 mg per day of elemental calcium. The amount of vitamin D required is between 400 and 800 IU per day. In older adults, regardless of climate or exposure to sunlight, a daily supplement of ≥ 400 IU per day of vitamin D is recommended because skin changes that occur with aging result in less efficient use of ultraviolet light by the skin to synthesize vitamin-D precursors. Calcium plus vitamin D at different doses have been shown to increase or maintain bone density in postmenopausal women and to prevent hip as well as all nonvertebral fractures in older adults. The dietary intake of calcium for postmenopausal women in the United States averages 500 to 700 mg per day; thus, most American women require calcium supplementation to ensure adequate intake.

Pharmacologic Options

Estrogen Replacement Therapy

Estrogen replacement therapy (ERT) remains an important choice for the prevention of osteoporosis. In addition to the beneficial effect on bone, epidemiologic observations suggest that estrogen prevents cardiovascular disease and may also reduce the incidence of Alzheimer's disease. In case-control and cohort studies, ERT is associated with a 30% to 70% reduction in hip-fracture incidence. Multiple studies have demonstrated that postmenopausal estrogen use prevents bone loss at the hip and spine when initiated within 10 years of menopause. However, in a cross-sectional study, BMD in women who initiated hormone replacement therapy (HRT) after age 60 years was found not to be significantly different from women who initiated HRT within 2 years of menopause. In the Postmenopausal Estrogen/Progestin Intervention trial, older women, women with low initial BMD, and women who had not previously used HRT were found to gain more bone than did young women, women with higher baseline BMD, and those who had previously used HRT. In the only prospective study of fracture prevention with estrogen, a decrease in incident vertebral fractures was seen in postmenopausal women using a transdermal preparation. The bone of women older than 70 years continues to be responsive to ERT, and data suggest that lower-than-usual doses of estrogen, when given with adequate calcium and vitamin D, are effective in reducing bone turnover and bone loss in older women. In a randomized, controlled study, women treated with 0.3 mg per day of conjugated equine estrogen plus 2.5 mg per day of medroxyprogesterone acetate were found to gain spine and hip BMD, whereas women treated with placebo showed no change. From the Study of Osteoporotic Fractures, separate analyses identified current estrogen use as a protective factor against hip fracture and demonstrated an increased risk of hip and vertebral fractures in women with undetectable serum estradiol levels. Thus, estrogen is useful for treatment of osteoporosis in older women, although it appears that lower doses can be recommended (see [Table 27.4](#) and [Table 49.1](#)).

In osteoporosis management, patients who do not respond to treatment may be identified either by BMD ($> 4\%$ per year loss at any site) or by fracture that occurs ≥ 3 months after initiation of treatment. If this situation arises in women who are taking ERT, then combination therapy with alendronate and ERT is indicated, unless the patient is not tolerating ERT. In two studies, ERT and alendronate have been shown to have an additive effect on BMD in comparison with either agent alone, although fracture data for combination therapy are not available.

Although estrogen can benefit several organ systems, its use by postmenopausal women has been limited by side effects and concerns about increased endometrial and breast cancer risk, and an unclear effect on cardiovascular disease risk (see [Hormone Replacement Therapy](#)).

Bisphosphonates

Alendronate has been approved for osteoporosis prevention and treatment. Women with osteoporosis who were treated with alendronate and compared with women on placebo were found to have increased bone density of the spine and hip, as well as decreased vertebral fracture rate. The Fracture Intervention Trial examined the effect of alendronate on postmenopausal women with severe osteoporosis, with or without vertebral fracture at baseline. Regardless of the presence of vertebral fractures at baseline, alendronate decreased vertebral fracture rate. In addition, alendronate resulted in a 50% reduction in hip fractures. A study in women aged 60 to 85 years indicated that an even lower dose of alendronate might be effective in older women. Further, data indicate that once-weekly dosing with alendronate (70 mg) is as effective in increasing spine BMD over 1 year as is daily dosing (10 mg) in postmenopausal women with osteoporosis (age range 42 to 95 years). Alendronate has also been approved for the prevention of osteoporosis in early postmenopausal women. The daily dose for prevention is lower—5 mg—than that given for the treatment of osteoporosis—10 mg. If treatment with alendronate alone is not effective, combining ERT with alendronate, which has an additive effect on bone density, may be indicated. In women with lesser degrees of osteoporosis, alendronate has not been shown to prevent hip fracture. Although alendronate has not been recommended for use in men, preliminary data from a prospective trial indicate that 10 mg per day increases bone mass in men, even those with low testosterone levels. Further, alendronate also prevents bone loss in men and women on glucocorticoids when it is initiated at the same time as the glucocorticoids.

The major side effects of alendronate are gastrointestinal, including abdominal pain, dyspepsia, esophagitis, nausea, vomiting, and diarrhea. Musculoskeletal pain may also occur. Esophagitis, particularly erosive esophagitis, may be seen most commonly in patients who do not take the medication properly. The absorption of oral bisphosphonates is very poor; thus, it is extremely important to provide specific and detailed instructions for patients receiving any bisphosphonate therapy ([Table 27.5](#)).

Risedronate, another bisphosphonate, has been approved for prevention and treatment of osteoporosis. In a 3-year study of postmenopausal women with ≥ 1 vertebral fracture at baseline, the cumulative incidence of new vertebral fractures was reduced by 41% (95% CI, 18% to 58%) in the group receiving risedronate (5 mg per day) rather than placebo. In addition, the incidence of nonvertebral fractures also decreased by 39% (95% CI, 6% to 61%) in the treatment group. BMD of the hip and spine increased significantly in the risedronate group. In the same study, 2.5 mg per day of risedronate was found to be ineffective and was discontinued after the first year of the study. Withdrawals because of side effects and any upper gastrointestinal adverse events were similar in the risedronate and placebo groups.

Etidronate was shown to increase spinal bone mass and decrease vertebral fractures in two studies in the early 1990s, and a 5-year follow-up study demonstrated continued benefit. Etidronate was given intermittently—400 mg per day orally for 14 days, and then stopped for 2.5 months—in these studies because continuous high doses can impair mineralization and produce osteomalacia. However, etidronate is not approved for use in treating osteoporosis because the data supporting fracture reduction were not sufficient. A separate study indicated a role for etidronate in preventing bone loss in patients who require long-term glucocorticoids.

Selective Estrogen Receptor Modulators

The selective estrogen receptor modulators are agents that act as estrogen agonists in bone and heart, but act as estrogen antagonists in breast and uterine tissue. These medications have the potential to prevent osteoporosis or cardiovascular disease without the increased risk of breast or uterine cancer. Tamoxifen, an agent used to treat breast cancer, has beneficial effects on bone, as reported in several studies, but it also has stimulatory effects on the uterus. Thus, tamoxifen is not indicated for osteoporosis treatment or prevention.

Raloxifene has been approved for the treatment and prevention of osteoporosis in postmenopausal women. Comparison of raloxifene with placebo in postmenopausal women with osteoporosis found that raloxifene decreased bone turnover and maintained hip and total body bone density. There were no differences between groups in breast abnormalities or endometrial thickness. Most importantly, data demonstrate that raloxifene (60 mg per day) reduces incident vertebral fractures by about 60%, despite only modest increases in bone density. Raloxifene was not found to significantly reduce nonvertebral, hip, or wrist fractures in this study. Reported side effects with raloxifene include flu-like symptoms, hot flashes, leg cramps, and peripheral edema.

Another important finding with raloxifene was a reduction in breast cancer in women who participated in the Multiple Outcomes of Raloxifene Trial. When women receiving raloxifene were compared with women receiving placebo, the relative risk for women receiving raloxifene of developing breast cancer was found to be 0.24 (95% CI, 0.13 to 0.44). In the same study, raloxifene was not found to increase the risk of endometrial cancer but was found to increase the risk of venous thromboembolic disease. In other studies, raloxifene was found to decrease total and low-density lipoprotein cholesterol and lipoprotein(a) levels without affecting high-density lipoprotein cholesterol or triglyceride levels. Thus, in clinical trials to date, raloxifene appears to be beneficial to several organ systems, although further study is required with regard to cardiovascular diseases and breast cancer prevention.

Calcitonin

Calcitonin is a hormonal inhibitor of bone resorption used to treat osteoporosis. It is available as a subcutaneous injection and as a nasal spray. The nasal spray has fewer reported side effects and greater patient acceptance, but it may be less effective. Calcitonin has been shown to increase bone density in the spine and reduce vertebral fractures. In epidemiologic studies, calcitonin has been shown to reduce hip fractures, although in clinical trials, hip bone density has not been found to increase. Preliminary analysis of a 5-year study demonstrated that the incidence of vertebral fractures in women receiving 200 IU per day of nasal spray calcitonin was lower than that of women on placebo. The reduction in hip-fracture incidence was not statistically significant in the group receiving calcitonin in comparison with the placebo group. Doses of 100 and 400 IU per day were studied as well, but they did not reduce incidence of vertebral fractures. In the same study, BMD changes at 3 years and changes in markers of bone turnover in the treatment and placebo groups were found not to be significantly different. Although there are no direct comparisons, calcitonin appears to be less effective than other antiresorptive drugs. There is some evidence that calcitonin produces an analgesic effect in some women with painful vertebral compression fractures.

Investigational Agents

Other bisphosphonates currently under investigation for the treatment and prevention of osteoporosis include pamidronate, ibandronate, and tiludronate. New selective estrogen receptor modulators are also being tested for use in osteoporosis treatment.

PTH, although leading to increased bone resorption when continuously elevated, can increase bone mass, trabecular connectivity, and mechanical strength when administered intermittently. PTH has been shown to increase spinal BMD in osteoporotic men and women. In a 3-year randomized study of postmenopausal women with osteoporosis, the group receiving estrogen plus intermittent PTH was found to have continuous increase in spinal bone mass over the study period, as well as decreased vertebral fracture rate. Bone mass of the hip and total body also increased significantly in the estrogen-plus-PTH group, in comparison with the group on estrogen alone.

The use of fluoride to treat osteoporosis is appealing because fluoride results in a large increase in spine bone density; however, the increase in BMD has not been found to be consistently associated with a decrease in vertebral fractures. In fact, in one study, the group receiving fluoride therapy was found to have a higher rate of appendicular fractures. Slow-release fluoride therapy has been found to be associated with an increase in spine BMD, as well as decreased incidence of vertebral fractures. Further studies are required before slow-release fluoride can be recommended for the treatment of osteoporosis.

The use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may also affect bone. This class of medication is commonly prescribed for the management of hypercholesterolemia and has been shown to stimulate bone formation in animals. Preliminary epidemiologic data suggest that the use of statins is associated with decreased incidence of fracture. Further information is required before these agents can be recommended for osteoporosis management.

WORKING WITH THE PATIENT

Establishing and maintaining an optimal regimen usually requires considerable discussion with individual patients and is much easier if patients are well informed. The use of educational materials can be quite helpful, as can the efforts of a nurse or other office personnel. Effective prevention and treatment of osteoporosis is possible, if the patient and clinician work together in a sustained fashion.

The osteoporosis patient's adherence to the medication regimen is important. Baseline and follow-up BMD measurements (every 1 to 2 years) are important to assess response to therapy; these measurements may also improve adherence by providing visual information regarding the effectiveness of the therapy. Another way to inform patients about their response to therapy is to measure markers of bone resorption. In particular, adequate estrogen and bisphosphonate therapy will almost certainly decrease the levels of urine or serum markers of bone resorption within 3 to 6 months.

MANAGEMENT OF VERTEBRAL FRACTURES

Most vertebral fractures are asymptomatic and are diagnosed by spinal radiographs. Over time, one may notice decreased height, increased kyphosis, or simply the fact that clothes no longer fit the person properly. Many older adults have chronic back pain due to the changes in the spine that occur with vertebral compression. In the case of symptomatic vertebral compression fractures, adequate pain control is essential. The pain usually lasts 2 to 4 weeks and can be quite debilitating. Nonsteroidal anti-inflammatory drugs and calcitonin can be tried; narcotics are commonly required to control the pain. Physical therapy is an important part of osteoporosis treatment programs for management of acute and chronic pain, as well as for patient education. The physical therapist can provide postural exercises, alternative modalities for pain reduction, and information on changes in body mechanics that may help prevent future fractures. Support groups for patients with osteoporosis are also important.

OSTEOMALACIA

Osteomalacia, an impairment of bone mineralization, is much less common than osteoporosis and can be definitively diagnosed only by bone biopsy. The clinical syndrome associated with osteomalacia consists of pain, myopathy, and fracture. The most common cause of osteomalacia in older adults is vitamin-D deficiency as a result of inadequate intake. In addition, excessive use of phosphate-binding antacids, chronic use of anticonvulsants, chronic renal failure, hepatobiliary disease, and malabsorption syndromes may also result in osteomalacia. The use of high-dose etidronate and fluoride may cause osteomalacia, albeit rarely. The symptoms of osteomalacia may be subtle, and thus the diagnosis may be delayed. Patients typically complain of diffuse bone pain and tenderness, proximal muscle weakness, and generalized fatigue. A characteristic waddling gait may result from the hip pain and thigh weakness. Laboratory studies typically demonstrate an elevated alkaline phosphatase, low phosphate, low or normal calcium, and low 25(OH)D levels. Plain radiographic films may show osteopenia or characteristic pseudofractures, most commonly seen in the proximal femur.

Osteomalacia is managed by treating the underlying cause. If vitamin-D deficiency is diagnosed, repletion can be accomplished with oral vitamin D, 1000 IU per day. Hypophosphatemia is corrected by the use of neutral phosphate salts, 500 mg four times daily. Patients on long-term anticonvulsant therapy may be supplemented with 400 to 800 IU of vitamin D daily. Osteomalacia due to hepatobiliary disease or chronic renal failure is managed with supplemental 25(OH)D and 1,25(OH)₂D, respectively.

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This was a randomized, placebo-controlled study comparing the effect of alendronate (10 mg per day), conjugated equine estrogen (CEE, 0.625 mg per day), or combination treatment on bone density and bone turnover in postmenopausal women ($N = 425$, mean age 62 years). All the women received 500 mg per day of calcium supplementation. By 6 months of the study, all treated groups experienced increased bone density at all sites. At the end of 2 years, the mean increase in bone mineral density of the spine, femoral neck, and total body was similar in the alendronate and CEE groups. The mean increase at the spine and femoral neck in the group treated with alendronate plus CEE was found to be greater than in either group receiving one treatment alone. Bone histomorphometry, at baseline and after 18 months of treatment, was also completed on nearly 100 participants and demonstrated decreased bone turnover but normal mineralization and normal bone quality in all treated groups. The authors conclude that

the combination of CEE and alendronate has an additive effect on bone density in postmenopausal women with low bone mass.

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The Study of Osteoporotic Fractures is a prospective cohort study of white women aged 65 years and older. This study compared baseline endogenous sex hormone levels in 133 women who subsequently had a hip fracture, 138 women who subsequently had a vertebral fracture, and randomly selected control women from the same cohort. The sex hormones measured were estradiol, estrone, sex-hormone-binding globulin (SHBG), and free testosterone. Parathyroid hormone, 25(OH)D, and 1,25(OH)₂ levels were also measured. The relative risk of either hip (RR 3.3 [1.9 to 5.9]) or vertebral fracture (RR 2.9 [1.7 to 5.0]) was higher in women who had undetectable serum estradiol levels (< 5 pg/mL); any estradiol level greater than 5 pg/mL was equally protective. The risk of hip and vertebral fractures also increased with increasing concentrations of SHBG. Both of these associations were independent of bone mineral density measurements. If women had estradiol levels < 5 pg/mL and SHBG levels > 1 µg/L, the risk of hip fracture increased 14-fold and the risk of vertebral fracture increased 12-fold. Hip, but not spine, fractures were associated with lower levels of 1,25(OH)₂ levels, but neither parathyroid hormone nor 25(OH)D levels were associated with hip- or spine-fracture risk.

- Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA.* 1999;282(7):637–645.

This was a multisite, randomized, placebo-controlled study evaluating the effect of raloxifene on the incidence of new vertebral fractures in postmenopausal women. More than 7000 women (mean age 67 years) with osteoporosis were randomly assigned to treatment with placebo, raloxifene 60 mg per day, or raloxifene 120 mg per day. All the women received 500 mg per day of calcium and 400 to 600 IU of vitamin D daily supplement. The outcome of primary interest was the incidence of vertebral fractures; the incidence of nonvertebral fractures, bone mineral density (BMD), and markers of bone turnover were also assessed. Treatment with raloxifene was found to reduce the relative risk of new vertebral fractures by 30% to 50%, depending on dose. The number of women needed to treat for 3 years to prevent one incident fracture was 46 for women with BMD-defined osteoporosis and 16 for women with baseline vertebral fractures plus low BMD. Raloxifene was not found to have an effect on rates of nonvertebral fractures, specifically wrist, ankle, or hip fractures. Raloxifene, at both doses, was found to significantly increase BMD at the hip and spine by 3% and 2%, respectively, and to decrease markers of bone turnover. The only serious adverse event found was an increased risk of thromboembolic events; the relative risk was 3.1 (1.5 to 6.2) for the combined raloxifene groups. Breast cancer was less common in women receiving raloxifene (RR 0.3 [0.2 to 0.6]) at 40 months. The authors conclude that raloxifene reduces the risk of incident vertebral fractures in postmenopausal women with osteoporosis.

- Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA.* 1999;282(14):1344–1352.

This was a multisite study comparing the effect of a new bisphosphonate, risedronate, on the rate of new fractures with that of placebo. More than 2000 women (mean age 69 years) were randomly assigned to placebo, risedronate 2.5 mg per day, or risedronate 5.0 mg per day. All women received 1000 mg per day of elemental calcium, and women with 25(OH)D levels < 40 nmol/mL received vitamin D supplementation. In order to be eligible for the study, women had to have at least two radiographically identified vertebral fractures or one vertebral fracture and low spine bone mineral density (BMD). The outcome of primary concern was the incidence of new vertebral fractures as determined by yearly lateral thoracic and lumbar spine films. BMD and biochemical markers of bone turnover were also measured during the trial. The group receiving 2.5 mg per day was discontinued after 1 year. The 1- and 3-year relative risks of cumulative vertebral fracture were 0.35 (0.19 to 0.62) and 0.59 (0.43 to 0.82), respectively, for

the group receiving risedronate 5.0 mg per day. For nonvertebral fractures, the relative risk was 0.6 (0.39 to 0.94). Further, BMD of the spine, femoral neck, and femoral trochanter also increased over the 3-year study period; markers of bone turnover decreased 30% to 40% over the treatment period. Adverse events, including gastrointestinal adverse events, were similar in the 5.0-mg-per-day risedronate and placebo groups. The authors conclude that risedronate is an effective, safe treatment for osteoporosis in postmenopausal women.

- Lindsay R, Cosman F, Lobo RA, et al. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. *J Clin Endocrinol Metab.* 1999;84(9):3076–3081.

In this study women ($N = 428$, mean age 62 years) with low bone density who had been on hormone replacement therapy (HRT) for at least 1 year (mean duration 9.2 years) were randomly assigned to additional treatment with either placebo or alendronate for another year. All the women were evaluated for calcium intake and were given supplements to assure an intake of 1000 mg per day; vitamin D supplementation of 400 IU was also provided to all. The outcome of primary interest was bone mineral density (BMD) of the spine and hip. The authors also evaluated the response to treatment of two markers of bone turnover, bone alkaline phosphatase and N-telopeptides of type I collagen. The group that received alendronate plus HRT had a 3.5% increase in spinal BMD and 2.5% increase in trochanteric BMD; no significant change was found in femoral neck BMD. Markers of bone turnover were also found to have further decreased in the group receiving alendronate plus HRT. The authors suggest that women on long-term HRT would benefit from additional BMD testing, and that if BMD is low, the clinician should consider the addition of alendronate treatment to further reduce bone loss.
- Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 2000;343:604–610.

A 2-year double-blind, placebo-controlled trial of 10 mg of alendronate daily was carried out in 241 men with osteoporosis who were aged 31 to 87. Men with secondary causes of osteoporosis except for low serum testosterone were excluded from the study; 36% of the men studied had a low testosterone level. After 2 years, men in the alendronate group showed a 7.1% increase in bone density at the lumbar spine, but those in the placebo group showed a 1.8% increase. Comparison also showed significant increases in bone marrow density of the hip, trochanter, and femoral neck in the experimental group over the placebo group. On follow-up radiographs, 7.1% of the men in the placebo group were found to have sustained a vertebral fracture, whereas 0.8% in the alendronate had a fracture (number needed to treat to prevent one fracture = 16). These results are comparable to the effects of alendronate observed in women and in persons with glucocorticoid-induced osteoporosis.
- Prestwood KM, Thompson DL, Kenny AM, et al. Low dose estrogen and calcium have an additive effect on bone resorption in older women. *J Clin Endocrinol Metab.* 1999;84(1):179–183.

This was a short-term controlled study examining the effect of 17β -estradiol plus calcium on biochemical markers of bone turnover in older women (mean age 75 years). Older women were randomly assigned to receive either 12 weeks of treatment with 0.5 mg per day of 17β -estradiol or 1300 mg of elemental calcium plus 800 IU of vitamin D per day. In the second 12 weeks of the study, the two treatments were combined in both groups. The control group did not receive any treatment over the 24-week study. The outcome of primary interest was serum and urine biochemical markers of bone turnover measured at baseline, and at 12, 24, and 36 weeks. This study demonstrated that low-dose estrogen and calcium have an additive effect on markers of bone resorption but not on markers of bone formation. Markers of bone turnover did not change in the control group. The authors suggest that estrogen replacement therapy at a lower than usual dose may be used for osteoporosis treatment in older women when they are given adequate amounts of calcium and vitamin D.
- Recker RR, Davies KM, Dowd RM, et al. The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women: a randomized, controlled trial. *Ann Intern Med.* 1999;130(11):897–904.

This was a 3-year randomized, placebo-controlled study examining the effect of 0.3 mg per day of conjugated equine estrogen plus 2.5 mg per day of medroxyprogesterone acetate on bone density in older women. All women received calcium supplementation. At baseline, serum 25(OH)D levels were measured in all the women, and those with levels < 30 ng/mL were supplemented with cholecalciferol to attain serum levels > 30 ng/mL. The outcome of primary interest was bone mineral density of the spine and hip. Markers of bone turnover and endometrial changes were also assessed. The study demonstrates that low-dose estrogen plus progesterone increase spine and hip bone mineral density in women who also receive adequate calcium and vitamin D supplementation. Markers of bone turnover in the treatment group also decreased during the treatment period, and endometrial changes were not found to be significantly different from those seen in the placebo group. The authors conclude that lower than usual doses of estrogen may be useful for the management of osteoporosis in older women.

- Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. *Aging (Milano)*. 2000;12(1):1–12.

This 1-year randomized, double blind study compared three dosing regimens of alendronate: 70 mg once weekly, 35 mg twice weekly, and 10 mg daily. All participants were postmenopausal women with osteoporosis. The primary end point was spine bone mineral density (BMD); secondary end points were hip and total body BMD and changes in biochemical markers of bone turnover. The results demonstrate equal efficacy in increasing spine BMD among all treatment groups and show fewer serious upper gastrointestinal side effects and a trend toward lower esophageal side effects with once-weekly dosing. The authors conclude that once-weekly dosing of alendronate (70 mg) is more convenient for patients and is a therapeutically equivalent alternative to daily dosing.

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