

Osteoporosis: Current Modes of Prevention and Treatment

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Abstract

The most common metabolic bone disorder is osteoporosis, which affects 25 million Americans, of whom 80% are women. Bone loss in women occurs most commonly after menopause, when the rate of loss may be as high as 2% per year. Bone mass can be determined with dual-energy x-ray absorptiometry. The rate of active loss can be assayed by the detection of bone collagen breakdown products (e.g., N-telopeptide, pyridinoline) in the urine. Although it has been suggested that white women are most commonly affected, Hispanic and Asian women are also affected. Strategies for the prevention and treatment of osteoporosis are directed at maximizing peak bone mass by optimizing physiologic intake of calcium, vitamin D therapy, exercise, and maintenance of normal menstrual cycles from youth through adulthood. Coupled with drug therapy should be a comprehensive approach to exercise and fall prevention. Stretching, strengthening, impact, and balance exercises are effective. Of the balance exercises, tai chi chuan has proved to be the most successful in decreasing falls. Prevention of bone loss is obviously preferable to any remedial measures, but new therapeutic strategies provide a means of restoring deficient bone.

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Osteoporosis is a common disorder affecting both women and men that leads to fragility fractures.^{1,2} Based on the World Health Organization (WHO) criteria,³ about a third of white women over age 65 have osteoporosis. Approximately 20% of white women past the age of 50 have osteoporosis of the hip, and 16% have osteoporosis of the vertebral bodies; rates for Hispanic and African-American women are lower.

The two most important risk factors for osteoporosis are insufficient bone mass at the time of skeletal maturity and rapid loss of bone after menopause. If a subject's bone mass is 1 SD less than the mean value for peers, the risk of hip fracture is increased 2.5-fold

and that of spine fracture is increased 1.9-fold. Fractures in elderly individuals are due in most part to reduced bone mass. The lifetime risk of any fracture among white women after the age of 50 approaches 75%, with the risk of hip fracture being 17% in white women, compared with 6% in white men. The lifetime risk of clinically evident vertebral fracture is 16% among white women. The remaining 42% of fractures occur in the proximal humerus, wrist, knee, and ankle. The risk of any osteoporotic fracture increases exponentially with aging in both men and women of all races, and in women the incidence of a vertebral body fracture increases sixfold from menopause to age 85.

A recent study demonstrated that the prevalence of a vertebral body fracture is equal among men and women when data are corrected for age.⁴ It appears greater in women because they have a higher survival rate than men. Osteoporosis that results from either limited peak bone mass or rapid bone loss with aging is the result of complex genetic and environmental effects (Table 1).

A number of risk factors, alone or in combination, are sufficient to reliably predict the bone density of an individual patient. Cummings et al⁵ has identified several factors that appear to be independent of bone mass. These include low body weight, recent weight loss, history of fractures, family history of fractures, and smoking. Although there is an association of

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Table 1
Factors in Skeletal Fragility Status

Factor	Increase in Risk of Fragility Fracture*
Bone density[†]	
Normal (0-0.9 SD)	0
Decreased bone mass (1.0-2.5 SDs)	+
Osteoporosis (>2.5 SDs)	+ / ++
Severe osteoporosis (>2.5 SDs + fragility fracture)	++
Rate of current bone loss[‡]	
Normal	0
High-normal	+
Greater than normal	++
Independent risk factors for fragility fractures	
History of low-energy fracture in parent or sibling	+
History of low-energy fracture	++
Body weight <85% of ideal weight	+ / ++
Recent 10-lb weight loss	+ / ++
History of smoking	+
Medications (corticosteroids, chemotherapy)	+ / ++

* Symbols: + indicates risk of bone loss; ++ indicates high risk of bone loss.
[†] Determined, according to WHO criteria, on the basis of the deviation from ideal peak bone mass in the spine or hip, whichever is lower.
[‡] Evaluated on the basis of detection of bone collagen breakdown products (e.g., pyridinoline, deoxypyridinoline, N-telopeptide).

low body weight and bone mass, the former appears to be an independent risk factor.

Osteoporosis has become an increasingly costly medical disorder due to the aging of the population.² More than \$13 billion was spent in 1995 for approximately 400,000 fracture-related hospitalizations and 180,000 nursing home admissions. Two thirds of the total amount was spent on patients with hip fractures. Even with current interventions, it is anticipated that hip fractures will increase threefold by the year 2040.

This article will address the current therapeutic options available to the orthopaedist for the prevention and treatment of osteoporosis. The physician now has an array of efficacious therapies. The field is progressing rapidly, and soon-to-

be released agents will also be discussed.

Definitions

The WHO developed a definition of osteoporosis to facilitate demographic and epidemiologic studies.³ Members of that group did not intend the definitions to be thresholds for therapeutic intervention. Individuals with low bone mass but without additional risk factors have very little chance of incurring an osteoporotic fragility fracture. In contrast, individuals with more modest loss of bone but with a large number of risk factors may have a much greater propensity to fracture.

The WHO utilized dual-energy x-ray absorptiometry (DXA) as a

method of establishing bone mass. Bone mass values were compared with the ideal peak bone mass in a pool of premenopausal women. Although skeletal bone mass is usually fairly uniform, there are often deviations, particularly those produced by the presence of other osseous changes, such as osteophytes about the spine, that may obscure generalized osteoporosis.¹ The bone mass is measured in the hip and the spine, and the bone density is operationally defined from the lower value. If the bone mass is within 1 SD of the ideal peak bone mass, the subject is considered to have normal bone. If the bone mass is 1 to 2.5 SDs below peak bone mass at either site, the subject is considered to be osteopenic or to have mild to moderate bone deficiency. Individuals with a bone mass more than 2.5 SDs below the ideal peak bone mass would be considered osteoporotic with marked bone deficiency, and those with a fragility fracture are considered to have severe osteoporosis.

Low body weight, recent loss of body weight, history of fragility fractures, history of fracture in the family, and a history of smoking are all considered to be high positive risk factors.⁵ Subjects with any of these factors have a greater risk of fracture regardless of bone mass. The absence of any of these risk factors diminishes the risk of fragility fracture. All fracture sites (e.g., phalanges, vertebral bodies, and long bones) appear to carry the same predictive power for subsequent osteoporotic fractures.⁵

Diagnosis

Bone density determination⁶ is indicated for both perimenopausal and postmenopausal women to determine their need for hormone replacement therapy, as well as for

patients with known metabolic bone disease or a high number of osteoporosis risk factors. It is also indicated to assess the effects of medications that affect the skeleton and to monitor the efficacy of osteoporosis treatment. Therapeutic prescriptions are usually based on DXA assessment and the WHO definition of osteoporosis. A bone density measurement from one site best predicts the fracture risk at that site. The proximal femur is the best site for predicting hip fracture risk. There is variability between machines, and results may be altered by the presence of other osseous changes, such as degenerative disk disease and osteoarthritis of the posterior elements. Present efforts to standardize the results obtained with different instruments may decrease some of the variability in bone density measurements.

The quantitative computed tomographic bone scan measures the most metabolically active bone. However, it entails more radiation and is less precise than DXA except in the most experienced hands. Ultrasound not only measures bone mass but also evaluates the characteristics that reflect bone quality, such as connectivity. Ultrasound of the calcaneus only moderately correlates with spine and hip bone mass due to either different methodology or the distance from those sites. Because of its ease of use, it may become an excellent tool for preliminary screening. However, its precision has not proved sufficient for monitoring patients undergoing treatment.

Currently, DXA and other similar instruments can measure bone mass but cannot determine at a single examination whether the mass is stable, increasing, or decreasing. Recent advances in biochemical markers provide this additional tool.^{1,7} Measurements of collagen cross-link degradative products,

such as urinary N-telopeptide, pyridinoline, and deoxypyridinoline peptides, now afford the clinician the ability to determine the rate of bone resorption. They also provide a convenient index of whether a chosen therapy is successfully curtailing bone loss. In addition, there are several markers for determining bone formation, including the serum alkaline phosphatase and osteocalcin concentrations.

Thus, the physician now has the ability to determine bone mass, the rate of turnover, and the fracture risk. Skeletal bone mass can be evaluated with DXA; the rate of bone resorption can be determined by assessment of collagen-degradation urinary products; and the weight status, fracture history, and history of smoking can be used to predict whether the patient is at average, above-average, or lower-than-average risk for fragility fracture.

To choose the correct medical management of a patient with osteoporosis, one should first rule out secondary causes and then decide whether the osteoporosis is a high- or low-turnover condition.¹ Secondary causes of bone thinning fall into the categories of bone marrow abnormalities, hormone abnormalities, and osteomalacia. Bone marrow abnormalities involve marrow space enhancement due to underlying marrow expansion. Multiple myeloma is a common example.

Endocrinopathies include hyperthyroidism, hyperparathyroidism, type I diabetes, and corticosteroid-induced osteoporosis. Hyperthyroidism frequently is an iatrogenic manifestation of overtreatment of a dysfunctional thyroid. Primary hyperparathyroidism is usually manifested by kidney stones, gastrointestinal complaints, and, most commonly, hypercalcemia. Spontaneous Cushing's syndrome is rare;

the overwhelming majority of cases of steroid-induced osteoporosis are iatrogenic secondary to treatment of a large spectrum of disorders. The effects of steroid therapy include decreased calcium absorption across the gut, increased urinary excretion of calcium, low osteoblastic bone formation, and enhanced osteoclastic resorption. Besides lowering the steroid dose, treatments include the use of active vitamin D metabolites (to increase calcium absorption), calcium-retaining diuretics, and antiresorptive agents.

Osteomalacia is frequently manifested in individuals with low body weight due to poor nutritional status and in those with inadequate sun exposure. It has been reported to occur in 4% to 8% of patients who present with hip fractures at northern US hospitals.¹ Chemical markers of this disorder are low-normal serum calcium and phosphorus levels, low 25-hydroxyvitamin D, secondarily elevated parathyroid hormone (PTH), elevated alkaline phosphatase, and low urinary calcium.

Once the secondary causes of osteoporosis have been eliminated, attention should be directed toward determining whether the patient has high- or low-turnover osteoporosis. In high-turnover osteoporosis, osteoclastic bone resorption is enhanced and is associated with more and deeper Howship's lacunae in bone. The osteoblasts are unable to fully refill the resorption cavities, resulting in a gradual loss of bone mass. This has been presumed to be the primary form of osteoporosis that occurs at menopause, although a segment of the elderly female population will still manifest high-turnover dynamics. The diagnosis of high-turnover osteoporosis is suggested by a high level of collagen cross-link degradation products, most notably N-telopeptide and pyridinoline peptide.⁷

Low-turnover osteoporosis, which is most commonly seen in the elderly and in a subset of postmenopausal women with an underlying genetic collagen disease, represents a failure of the osteoblasts to form bone. Osteoclastic bone resorption is usually normal or may be slightly decreased, but the osteoblasts are profoundly diminished in terms of their metabolic activity. Collagen cross-link peptides are at a premenopausal level or lower, and bone formation markers, including bone alkaline phosphatase, are diminished.

General Treatment Principles

The most important principle in the treatment of osteoporosis is prevention. Two critical elements that determine fragility of bone as related to bone mass are the attainment of peak bone mass and the prevention of postmenopausal resorption.^{1,8} The attainment of peak bone mass is dependent on adequate caloric intake, physiologic calcium and vitamin D intake, normal menstrual status, and appropriate exercise. Episodes of amenorrhea or oligomenorrhea must be corrected; the physician should address the initiating events, which can include inadequate caloric intake, hormonal dysfunction, or exercise beyond the ability to maintain adequate caloric intake. Peak bone mass is achieved by the age of 25. Bone loss can result from hormonal dysfunction or weight loss. Weight should be maintained at normal levels throughout life in spite of societal pressures to be thin. Calcium and vitamin D should be maintained at levels appropriate for age. Exercise should be directed at impact loading, muscle strengthening, and balance training.

If bone loss occurs despite physiologic preventive measures, as

demonstrated by low bone mass on DXA study and/or increased levels of bone collagen degradative products, therapy should be considered. The specific form of therapy and the point of intervention will depend not only on the bone mass of the individual but also on risk factors and bone dynamics. Each of the current modes of prevention and treatment for osteoporosis (Table 2) will be discussed in depth.

The therapeutic agents currently available for the treatment of osteoporosis largely fall within the area of antiresorptive agents and are directed toward high-turnover osteoporosis. Antiresorptive agents include hormone replacement therapy (estrogen, tamoxifen, and

raloxifene), the bisphosphonates, and calcitonin. Calcium and vitamin D are also weak antiresorptive agents. The Food and Drug Administration (FDA) has not yet approved any bone stimulatory agent. However, there has been keen interest in the use of sodium fluoride and, most recently, PTH and PTH-related peptide analogs as agents that directly stimulate osteoblastic bone formation.

Calcium

There is evidence of an increasing prevalence of calcium and/or vitamin D deficiency in the general population.^{1,8} Frank osteomalacia has been identified in a small but

Table 2
Treatment Protocols

For men and premenopausal women
Physiologic calcium (see Table 3)
Vitamin D (400-800 U/day)
Adequate nutrition
Exercise (impact exercises, strengthening, and balance training)
For postmenopausal women*
Antiresorptive agents
Estrogens (with progestin if uterus is intact)
Alendronate (Fosamax), 5 mg/day for mild to moderate bone deficiency; 10 mg/day if bone mass is 2.0 SDs below peak bone mass
Calcitonin (Miacalcin), 200 U/day via nasal spray for mild bone loss, new fractures, bone pain
Pamidronate (Aredia; intravenous infusion), approved for Paget's disease and osteolysis associated with malignancy
Raloxifene (Evista), an antiestrogen (SERM) approved for prevention Not approved by FDA (experimental)
Etidronate (Didronel), cycle of 400 mg/day for 2 weeks, rest 11 weeks; approved for Paget's disease
Tamoxifen (Nolvadex; antiestrogen agent), 70% as effective as estrogen, used in treatment of breast cancer
Formative agents (experimental)
Monofluorophosphate (Monocal; fluoride and calcium supplement), 24 mg of elemental fluoride per day, used as a nutritional additive
Slow-release sodium fluoride, under study

* Earlier intervention if the bone loss rate is increased and/or there are independent risk factors.

definite population of hip fracture patients from several parts of the United States, and many other elderly persons have secondary hyperparathyroidism. Sixty-five percent of women past the age of menopause have varying degrees of lactose intolerance and by preference avoid lactose-containing dairy products. There is also constant pressure on the public to be thin, and calcium-containing products, most notably milk, are perceived to have high caloric densities. Consequently, whether by choice, habit, or design, most Americans have calcium intakes below the recommended level, particularly in the elder years. Even with detailed instruction and guidance, it is difficult for Americans to obtain adequate amounts of calcium (specifically, 1,500 mg daily) strictly from their diet.⁸ Therefore, addition of calcium-containing supplements is required if age-corrected physiologic calcium intake is to be achieved. In 1994 a National Institutes of Health consensus development panel established recommended daily levels of calcium intake (Table 3).⁹

Calcium is best assimilated when taken throughout the day, with no dose being larger than 500 mg at a given time. Although there are multiple forms of calcium, those most commonly chosen are calcium carbonate and calcium citrate.

Calcium carbonate contains 40% elemental calcium and requires acidity to be solubilized. Therefore, it should be taken with foods. Its benefits are compromised when ingested with a meal of fried foods or heavy fiber. Achlorhydric individuals will not absorb calcium carbonate. The side effects of calcium carbonate intake include a sensation of gas and constipation.

Calcium citrate is 21% elemental calcium and will dissolve even in the absence of acidity. It does not

Table 3
Recommended Daily Calcium Intake*

Age Range	Recommended Dietary Allowance, mg/day [†]	Suggested Dietary Intake, mg/day ⁹
Infants		
Birth to 6 months	400	400
6 months to 1 year	600	600
Children		
1-5 years	800	800
5-10 years	800	800-1,200
Adolescents and young adults (11-24 years)		
	1,200	1,200-1,500
Female athletes		
Euestrogenemic	NS	1,000
Hypoestrogenemic	NS	1,500
Adults		
Men (25-65 years)	800	1,000
Women (25-50 years)	800	1,500
Pregnant/nursing mothers	1,200	1,200-1,500
Postmenopausal women		
Receiving HRT	NS	1,000
Not receiving HRT	NS	1,500
Over 65 years (both sexes)	800	1,500

* Abbreviations: HRT = hormone replacement therapy; NS = not specified.

† Adapted from Subcommittee on the Tenth Edition of the Recommended Dietary Allowances, National Research Council: *Recommended Dietary Allowances*, 10th ed. Washington, DC: National Academic Press, 1989.

form gas and tends to ameliorate constipation. Calcium citrate is chosen for those individuals who are achlorhydric, and it decreases the risk of kidney stones.¹⁰

The other forms of calcium appear to hold no benefit over calcium carbonate and calcium citrate. Calcium phosphate delivers a high phosphate load that can aggravate preexisting secondary hyperparathyroidism. Other forms of calcium frequently contain minimal amounts of elemental calcium and require a high dosage to achieve physiologic efficacy. Care should be taken regarding the origin of the calcium, as some forms have measurable levels of lead and arsenic (e.g., bone meal).

Magnesium is often supplied in conjunction with calcium. With reasonable diets, magnesium deficiency is rare, and added magnesium is not required to improve absorption. However, magnesium can ameliorate the tendency toward constipation.

Dietary sources of calcium include dairy products, broccoli, tofu, and rhubarb. Because it is extremely difficult to obtain 1,500 mg of calcium a day solely from food products, most dietary experts recommend taking a careful history to determine the actual amount of calcium ingested by the individual through normal dietary choice and then adding sufficient supplements to reach the goal.

When individuals taking calcium are compared with a placebo historical group who are not taking calcium, there is clear evidence that calcium supplementation is associated with a lower rate of bone loss.^{11,12} However, at menopause, calcium supplementation by itself will not prevent vertebral-body bone loss completely. A series of small population studies have shown marginal reduction in fracture incidence with calcium alone.^{11,12} In a study in which calcium with vitamin D was provided to a large group of ambulatory elderly women, Chapuy et al¹³ demonstrated a highly significant ($P<0.02$) 25% decrease in hip fracture rate and a similar decrease in nonvertebral fractures. In spite of the concern that vitamin D was part of that particular study, there is consensus in the metabolic bone community that calcium supplementation in itself can reduce fracture rates by at least 10%. Calcium lessens the rate of bone loss and appears to significantly decrease the fracture rate. Calcium is extremely cost-effective, and there is further evidence that calcium enhances the benefit of estrogen and probably the other antiresorptive agents. It is therefore highly recommended that everyone obtain recommended intakes of calcium.

Some individuals cannot tolerate desirable doses of calcium due to side effects of indigestion or constipation. In those circumstances, a lower level of calcium can be given (usually 500 mg), and absorption can be enhanced by co-utilization of 400 to 800 units of vitamin D or 0.25 μg of calcitriol. The efficacy of calcium supplementation can be demonstrated by the correction of secondary hyperparathyroidism.

After a major long-bone fracture, calcium is required for repair of the fracture and its ultimate remodeling. Physiologic calcium intake is critical.

Vitamin D

“Vitamin D” is a generic descriptor for a group of fat-soluble sterol vitamins that includes ergocalciferol (D_2) and cholecalciferol (D_3). The active metabolite is 1,25-dihydroxyvitamin D; 25-hydroxyvitamin D is considered a provitamin, which requires α -hydroxylation to become active. Vitamin D is critical for calcium absorption. The main evidence for its use as a preventive agent has been shown in individuals who are vitamin D-deficient. Rosen et al⁸ studied the data on a group of women in Maine, in whom almost all their bone loss occurred during the winter months, when their vitamin D levels were lowest. Institutionalized patients and individuals with poor dietary intake frequently are vitamin D-deficient.

In those individuals in whom vitamin D deficiency is clearly present, vitamin D supplementation will lead to enhanced bone mass and improved quality of bone. However, there is uncertainty about whether vitamin D per se in a vitamin D-competent individual can lead to enhanced bone mass. In a study of elderly French women, Chapuy et al¹³ provided both calcium and vitamin D, and, as previously noted, the hip fracture rate decreased by approximately 25%. The relative importance of vitamin D versus calcium could not be determined from that study.

Various forms of active vitamin D metabolites have been used in trials, including 1,25-dihydroxyvitamin D (calcitriol) and 1α -hydroxyvitamin D, among others. Gallagher and Riggs¹⁴ compared the effects of calcitriol versus placebo on the incidence of vertebral fractures in 62 postmenopausal subjects with osteoporosis. In 1 year, the vertebral fracture rate in the group receiving calcitriol was significantly lower than that in the placebo group (15% vs 32% [$P<0.05$]). Tilyard et al¹⁵ also

showed a very significant (50% [$P<0.05$]) improvement in fracture rate, compared with a placebo-control group, when calcitriol was given with calcium. However, in their study, the placebo group did extremely poorly, worse than historical controls.

There is a wide range of results in the data, making it impossible to arrive at an estimate of the benefit of treating vitamin D-competent individuals with supraphysiologic vitamin D supplementation. However, it is quite clear that in vitamin D-deficient individuals, vitamin D will increase bone mass and decrease the fracture rate.¹⁶ Consequently, it was the recommendation of a National Institutes of Health consensus conference⁹ that individuals should take between 400 and 800 units of vitamin D daily, particularly if they have poor dietary intake or increased risk factors for osteoporosis. It is a most cost-effective form of augmentation and at these levels is associated with essentially no major risk. However, individuals who take 50,000 units of vitamin D per week, a common practice, have an increased risk of the development of kidney stones, nausea, and other manifestations of hypercalcemia.

In choosing the vitamin D supplement, the time course of action should be taken into consideration. The half-life of both vitamin D_2 and vitamin D_3 is approximately 2 months, that of 25-hydroxyvitamin D is several days, and that of 1,25-dihydroxyvitamin D is only 4 hours. Because the shorter-acting vitamin D preparations are more costly, they may be preferred only in trying to establish the appropriate dosage for a patient with a measurable deficiency. Once the appropriate dose has been chosen and the underlying osteomalacia or deficiency has been treated, a change can be made to a cheaper, longer-acting form of vitamin D.

Estrogen

Estrogen is an essential factor in the prevention and treatment of osteoporosis.^{1,10,17-19} Osteoblasts have identifiable receptors for estrogen, as do a variety of cells that are found within the marrow, including the macrophage. The precise target cell for estrogen has not been identified. Estrogen has some indirect effects on mineral metabolism by increasing calcium absorption across the gut and by conserving renal calcium.

In the late 30s and early 40s, women's estrogen levels start to decline, although true estrogen deficiency does not become apparent until just prior to menopause. At that time, the follicle-stimulating hormone and luteinizing hormone values increase to stimulate higher estrogen productivity from the ovaries. When women enter menopause, their skeletal bone loss rapidly increases by approximately 2% per year (an 8% decline in the cancellous bone and a 0.5% decline in the cortical bone). The rapid bone loss begins to decrease after 6 to 10 years.

All studies have indicated that in 80% of individuals, the administration of estrogen to perimenopausal women during the rapid postmenopausal decline can decrease the loss in all bones, particularly those rich in trabecular bone (e.g., the vertebral bodies). Women on average will gain approximately 2% in bone mass per year, with a slowing down of this augmentation after several years of estrogen therapy. If estrogen therapy is terminated, there is rapid "catch-up" bone loss, so that approximately 7 years after estrogen cessation the bone mass approaches that in an individual who has never taken estrogen therapy.

The bone-sparing dose of estrogen is roughly 0.625 mg of conjugated equine estrogen or equivalent.

Lower levels may be sufficient for obese women, as androgens can be converted to estrogenlike products within the body fat. However, 0.625 mg may be insufficient for individuals who are very thin and for those who smoke, as estrogen degradation is increased by cigarette smoking. Estrogen works better when given in conjunction with 1,000 mg of calcium.

In addition to maintaining bone mass, estrogen has been shown in nonrandomized trials^{10,17-20} to decrease vertebral fractures by about 50% and hip fractures by 25%. There is an enhancement of the long-bone mass by estrogen, and after 10 years 75% of patients will have benefited by reduction of fractures. On the basis of studies of long-term use (10 or more years), estrogen might be expected to decrease the rate of all fractures by 50% to 75%.

Estrogen therapy may be taken orally, sublingually, transdermally, percutaneously, subcutaneously, or intravaginally. The usual route of hormone replacement in the United States is oral or transdermal. It is mandatory that women who have an intact uterus take a progestin along with the estrogen; those who have undergone a hysterectomy can take estrogen alone.

Estrogen has many nonosseous effects, some of which are quite beneficial. Estrogen can ameliorate certain primary symptoms of menopause, such as hot flashes and genitourinary tract atrophy. A 50% reduction in coronary artery disease, prevention of tooth migration, and prevention or postponement of Alzheimer's disease have also been reported. The unopposed use of estrogen will increase the chance of endometrial cancer, but this can be avoided by the use of either cyclical or continuously administered progestational agents. Replacement programs include cyclical estrogen and progestin,

constant estrogen and cyclical progestin, or both agents constantly. The latter is quite successful in women 5 or more years postmenopausal, but it has been associated with breakthrough bleeding in individuals closer to the beginning of menopause. In premenopause and early menopause, birth control pills are most effective and well tolerated.

The major concern with estrogen is the increased risk of breast cancer.^{10,17-19} In a questionnaire study of nurses,¹⁰ women who had been receiving estrogen for 5 years or more beginning before the age of 65 had up to a 30% greater risk of breast cancer than peers who were not taking estrogen. It has been estimated that 11 women per 100 will get breast cancer in their lifetime and that this number will be increased to 14 with the use of estrogen for 5 years, as in that study. However, more recent data in a 10-year follow-up study of the same nurse population indicated that total mortality among women who use postmenopausal hormones is lower than among nonusers, mainly due to reduced cardiovascular disease. The survival benefit diminishes with longer duration of estrogen use and is lower for women with a low risk of coronary disease. Current hormone users with coronary risk factors had the largest reduction in mortality rate, with substantially less benefit for those at low risk. Women taking estrogen-progestin combinations had a lower mortality rate than nonusers, even correcting for the increased risk of breast cancer. In that study, only those women who had been taking estrogen for over 10 years had an increased risk of breast cancer (up to 43% over peers).

In summary, the consensus is that hormone replacement therapy is extremely effective in enhancing

bone mass and preventing fractures. Women receiving hormone replacement therapy will live longer, but there is an increased risk of breast cancer. Unfortunately, the potential risk of cancer has frightened many women, so that in one large series,¹⁹ 50% or more of women took estrogen for less than 1 year before rejecting it.

A series of antiestrogens have been developed (originally aimed at combating breast cancer), which have been demonstrated to be beneficial to the skeleton. Tamoxifen,²¹ with the longest history, has been clearly shown to enhance survival after breast cancer, but it loses its benefit after 5 years. Animal studies and human data also demonstrate that in addition to inhibiting breast cancer, tamoxifen has a beneficial effect in improving the cardiac lipid profile and maintaining, if not increasing, bone mass. It is approximately 70% as effective as estrogen in terms of bone mass augmentation.

Tamoxifen has not found favor as a primary skeletal agent due to an increased risk of uterine cancer. Just as occurs with estrogen, termination of tamoxifen therapy will lead to rapid bone loss unless other agents are substituted. More than 50% of women receiving tamoxifen will suffer bothersome postmenopausal symptoms, such as hot flashes. Thus, tamoxifen is not the agent of choice for the treatment of osteoporosis, although women taking tamoxifen for breast cancer are protected from osteoporosis.

A new series of antiestrogens, known as selective estrogen-receptor modifiers, or SERMs, are currently being developed. Raloxifene is the furthest along in clinical trials and has already reached the market.²² It reduces the incidence of breast cancer by 50%. There may be a decrease in postmenopausal symptoms (25%) compared with tamoxifen, and it is very effective in

improving bone mass and preventing vertebral fractures.²³ Other similar antiestrogens also appear to overcome the threat of breast cancer and do not stimulate the endometrium and therefore should be much more widely accepted than the current estrogen therapy. Recent randomized trials have demonstrated efficacy in terms of vertebral fracture prevention with raloxifene.

Thus, it appears that hormone replacement therapy is an extremely effective method for maintaining bone mass and preventing fractures.^{10,17-22} Currently, women tend to consider estrogen therapy at the onset of menopause and then again when they are in their late 60s, when the risk of breast cancer has diminished and the nonskeletal benefits are markedly increased. It is an extremely cost-effective agent for the protection of the skeleton, but its use must be dictated by a total analysis of its skeletal and nonskeletal benefits and disadvantages. It is contraindicated for women with a strong family history of breast cancer or a personal history of thrombophlebitis or stroke. Women with none of those factors but with abnormal lipid levels would strongly benefit.

It should be remembered that when estrogens are terminated, there is rapid "catch-up" bone loss. In this setting, other antiresorptive agents should be utilized to maintain the benefit of estrogen therapy.

Calcitonin

Calcitonin is an FDA-approved antiresorptive agent.^{1,10,24-26} It is a non-sex, non-steroid hormone that specifically binds to osteoclasts and decreases their activity as well as their number. The various forms of calcitonin that are derived from salmon are 40 to 50 times more potent than the human form.

Until recently, calcitonin was administered only subcutaneously; however, nasal spray and rectal suppository forms have now been produced. Calcitonin should be given in conjunction with calcium. With prolonged use, nonhuman calcitonins can be antigenic, with long-term resistance developing in 22% of subjects who take them.¹⁰ The injectable form has been associated with a number of side effects, but the nasal form appears to be well tolerated, with rhinitis and sinusitis developing only in rare instances.

Unlike the other osteoporotic agents, calcitonin appears to have an analgesic effect, the physiology of which is not clearly defined.²⁷ Because of this analgesic effect, calcitonin is frequently used in patients with symptomatic acute vertebral fractures. No deleterious effect on fracture healing has been demonstrated. Therefore, administration can be initiated even in the earliest stages of fracture repair.

Current studies indicate that calcitonin is effective in stabilizing and increasing spinal bone mass in early- and late-postmenopausal women.^{10,24-26} There is little evidence at this time of augmentation of bone mass in cortical bone, especially in the hip. Overgaard et al²⁶ demonstrated a 75% reduction in vertebral fractures. However, the confidence limits in that study were extremely large. A recent prospective study suggests a decrease in the rate of vertebral fractures of 37% but no effect on hip fractures.²⁸ The data regarding nonvertebral fractures are inconclusive at this time, although one observational study found a 24% reduction in the hip fracture rate.²⁷ Thus, the benefits of calcitonin are still unclear.

Calcitonin appears to be most effective in treating high-turnover osteoporosis. It has also been used quite effectively in treating localized regional osteoporosis, particu-

larly if it is associated with increased bone turnover as evidenced by enhancement on bone scan. The usual dose is a single spray of 200 units daily in alternate nostrils. Calcitonin is a hypocalcemic agent and requires the co-utilization of physiologic levels of calcium intake. Calcitonin is used especially for painful osteoporosis and stress fractures.^{1,10} The long-term use of calcitonin and its possible benefit on nonvertebral fractures are still pending.

Bisphosphonates

Bisphosphonates are analogs of pyrophosphate in which the linking oxygen of the pyrophosphate is replaced with a carbon and various side chains. Etidronate, the first-generation bisphosphonate, has been in wide use for the treatment of Paget's disease and has reported efficacy in the treatment of osteoporosis.^{29,30} There are now second- and third-generation bisphosphonates in various stages of clinical trials and release for osteoporosis.^{1,10,31,32}

The major mode of action of bisphosphonates is binding to the surface of hydroxyapatite crystals, which inhibits crystal resorption, but there are also intracellular actions in osteoclasts. With the first-generation bisphosphonates, crystal formation is also inhibited. Second- and third-generation bisphosphonates have been tailored so that inhibition of resorption is 1,000 times greater than inhibition of formation at the therapeutic dosage. These agents are clearly effective in protecting the skeleton against resorption. Formation appears not to be a significant issue.

Alendronate, a third-generation bisphosphonate, has been tested in a canine fracture-healing model and has been found not to inhibit the repair process in a limited num-

ber of dogs.³³ However, this agent has not been tested in fracture healing in humans, particularly in the elderly, in whom all the physiologic resources may be somewhat compromised. Alendronate acts as an effective shield against osteoclastic bone resorption and has also been utilized in a model of osteolysis.³⁴ It has been shown to cause apoptosis of osteoclasts.

In the initial test of bisphosphonates in the treatment of osteoporosis, 400 mg of etidronate was given daily for 2 weeks, followed by a rest period of 11 weeks.^{1,10,30} At that dosage, bone mass increased 1% to 2% in the spine, and the incidence of fractures decreased in comparison with a group receiving calcium alone. However, after 2 years, the test group and the control group became indistinguishable in terms of fracture rate and bone mass. Further studies at various periods of time have been inconclusive. In light of the close coupling between formation and resorption with etidronate and the limited data for treatment beyond 2 years, the FDA has not approved this agent for osteoporosis. However, the Canadian government has given its approval for use of this drug.

Alendronate has gone through rigorous trials. In well-controlled random studies, alendronate at a dose of 10 mg per day produced an increase in bone mass of between 2% and 4% per year in the vertebral body and 1% to 2% per year in the area of the hip.^{31,32} Fracture rates declined approximately 50% at the spine, hip, and wrist after 1 year of therapy across the full spectrum of osteoporotic patients. A dose of 5 mg achieved about 85% of the yield of the 10-mg dose. The 10-mg dose has been approved for the treatment of osteoporosis as recommended by the FDA for patients with bone densities at least 2 SDs below peak bone mass, and has been approved at 5 mg per day for

the prevention of osteoporosis in cases of minor bone loss.

Alendronate has a prolonged half-life of 10 years (i.e., 50% of the absorbed bisphosphonate will be within the skeleton for 10 years). In light of this slow turnover and the uncertainty of the role that bisphosphonates may play in fetal development, the FDA has recommended against the use of this agent in women of childbearing age, particularly if they are pregnant. There have been no approved studies of the treatment of men. However, the consensus is that alendronate should work quite effectively in the male population. In analyzing the data from alendronate, it became apparent that regardless of bone mass gain, all subjects had the same degree of prevention of fractures. This suggests that another factor, such as a change in the quality of bone, may have accounted for at least part of the protection against fractures.

The original alendronate trial carefully excluded patients with gastrointestinal disorders.³⁵ The placebo group and the treated group had relatively the same amount of indigestion. However, it was noted that in a small number of individuals, use of alendronate led to esophageal ulcers, and in a nonselected population alendronate reportedly caused indigestion in as many as 30% of patients.³⁵ In the Metabolic Bone Disease Unit at the Hospital for Special Surgery, instead of using the full dose initially, patients are instructed to gradually increase the dose (one pill is taken the first week, two pills the second week, three pills the third week, and so on). With this regimen, 96% of patients were able to tolerate alendronate, although 5% of those individuals continued with a lower dosage (10 mg three times a week). The 5-mg dose has been recommended for prevention of osteoporosis. Several centers

have utilized 10-mg doses three times a week and have achieved the same benefit as with the 5-mg dose given daily.

Bisphosphonates demonstrate their efficacy by a rapid drop in urinary excretion of collagen cross-link peptides. Within 3 months of achieving a therapeutic dose, 90% of individuals will have a 30% drop in N-telopeptide level. This change is noted far earlier than improvement in serial bone-density DXA studies.

It is uncertain how long alendronate should be continued. There is now evidence that bone mass continues to improve for at least 4 years. Cessation of alendronate does not lead to the rapid bone loss that occurs after cessation of estrogen. Some data suggest that bone augmentation will continue for 3 to 6 months after cessation of the agent and then level off before a gradual decline.

Besides the complications of dyspepsia and esophagitis, alendronate has been associated with occasional episodes of diarrhea and bone pain, the latter particularly in those individuals who did not receive calcium supplementation before treatment. Therefore, it is recommended that calcium be given in addition to alendronate (but not at the same time, so as to allow better absorption of the bisphosphonate).

Several other bisphosphonates have received approval.³⁶ Pamidronate has been administered intravenously by oncologists to treat bone osteolysis due to tumors. It has been shown to be effective in decreasing pathologic fractures, although it has played no role in enhancing survival of patients with metastatic disease. It has been used selectively in patients with osteoporosis as an off-label agent. Tiludronate has been approved for use in the treatment of Paget's disease as an oral agent,

but has no benefit in the treatment of osteoporosis. Residronate, ibandronate, and several other bisphosphonates are at earlier stages of investigation.

Alendronate is therefore recommended as an excellent antiresorptive agent either as a treatment or as a preventive therapy. It does not provide the analgesic benefit of calcitonin and does not offer the nonskeletal benefits (and hazards) that are associated with estrogen. There is some suggestion, currently being tested in clinical trials, that alendronate and estrogen may be synergistic, as they have different sites of action.³⁷ If a patient has not responded to one of the agents, the addition of the other may result in a positive bone-accretion stage.

Bone-Stimulating Agents

Estrogen, calcitonin, and bisphosphonates primarily act by preventing bone resorption and are most effective in high-turnover osteoporosis. In low-turnover osteoporosis, where the primary failure is lack of osteoblastic bone formation, there is a need for agents that will directly stimulate osteoblastic function. Several agents under development appear to have a direct effect on the osteoblast and offer potential solutions to the low-turnover osteoporotic state. These experimental agents include fluoride, PTH, PTH-related peptide, and its analogs.

Sodium fluoride enhances the recruitment and differentiation of osteoblasts. The exact mechanism by which fluoride acts to stimulate osteoblastic bone formation is still uncertain. In both animal and human studies, when fluoride was given, bone mass formation was enhanced, particularly in the trabecular bone. At high doses, fluoridosis occurs, in which there is increased compressive strength but a diminution of bending strength.

Clinical studies have shown that fluoride treatment is very effective in increasing bone mineral density,³⁸ but initial studies from the Mayo Clinic, in which a high dose of sodium fluoride was used, suggested that fluoride was not effective in reducing the incidence of spine fractures in spite of increased bone mass.³⁹ Those investigators used a high dose of an immediate-release form of fluoride (75 mg/day). Subsequent studies in which a lower dose of fluoride was coupled with adequate calcium supplementation to mineralize the newly formed bone demonstrated that this combination could both increase bone density and decrease the fracture rate.⁴⁰

Two additional fluoride preparations have come into consideration, monofluorophosphate⁴¹ and slow-release sodium fluoride.⁴² With both forms, there is no high peak fluoride concentration in the blood, but rather a broad prolonged plateau of mild elevation, and bone augmentation has been clearly demonstrated without marked toxicity.^{41,42} Using a slow-release form at a dose of 50 mg of sodium fluoride per day, Pak et al⁴² found that the bone density in the spine increased 4% to 6% per year during the 4 years of the study, while that in the femoral neck increased 2% in the first 2 years. Furthermore, the incidence of vertebral fractures decreased significantly. In studies utilizing monofluorophosphate, particularly at doses of 15 mg of fluoride per day, there was a dramatic decrease in spinal fractures and an increase in bone mass.⁴¹ Neither of these agents has been associated with fluoridosis, stress fractures, gastrointestinal upset, or an increase in hip fractures.

All fluoride preparations require 1,500 to 2,000 mg of elemental calcium to allow appropriate mineralization of the fluoride-stimulated

bone.⁴³ Fluoride, particularly in its new forms, offers great potential for treatment of low-turnover osteoporosis.^{1,10,43} These fluoride preparations have not been approved by the FDA and should be considered experimental.

Parathyroid hormone has been given cyclically in a parenteral form to postmenopausal women. Patients demonstrated a clear enhancement of vertebral bone mass but a decline in the bone mass in cortical areas, especially in the hip.⁴⁴ These results are in contrast to the findings noted with parathyroid adenomas, in which the PTH concentration is elevated continuously. There is very little data on fracture prevention. Parathyroid hormone-related peptide and its myriad of analogs are being tested in animal and early clinical trials. The analogs appear to be potent stimulators of osteoblastic bone formation and may be quite effective even in the face of corticosteroid treatment. They are still in the extremely preliminary investigation stage at this time.

It appears that the first agents that will be available for direct bone stimulation are the fluorides, most probably in the form of slow-release sodium fluoride. Until broader experience has been gathered, it will be used in the United States as in Europe, largely as a salvage therapy for treatment of osteoporosis, particularly in patients with low-turnover states.

Exercise

Although exercise is not considered a medical modality, it is highly effective in favorably affecting the skeleton and preventing falls.^{45,46} Bone cells clearly sense their environment, and numerous studies have demonstrated that immobilization will lead to bone loss. The mechanism by which

exercise signals the cell is still to be determined. Low levels of exercise are critical for maintenance of bone mass. Higher levels will lead to modeling of the bone to adapt to its new environment, and even higher levels will lead to failure.

The optimal type and duration of exercise have not been established, although several investigators have demonstrated that a minimal amount of exercise of appropriate type may be sufficient to stimulate the osteoblasts for 24 to 48 hours. Bone mass is very closely correlated with the muscle mass acting on that bone. Thus, programs that are aimed at developing increased muscle strength will be translated into increased bone mass in the affected limb. The strength of a bone has been demonstrated to be related to the mass of the bone and the distribution of the mass. The latter is affected by exercise.

A number of studies have evaluated exercise in the prevention of bone loss after menopause.⁴⁷ A moderate level of exercise by an individual who receives an appropriate diet, with adequate calcium and vitamin D, can diminish the rate of bone loss. Load-bearing exercise is most effective in preserving or increasing skeletal mass. To be effective in altering bone density, the exercise must directly strain the skeletal sites. Exercise may be a mitigating factor, but it will not substitute for the antiresorptive agents. Exercise to the point of caloric drain or development of amenorrhea is associated with stress fractures and osteoporosis. The most profoundly affected patients, those with the triad of osteoporosis, amenorrhea, and anorexia, present with multiple stress fractures as well as osteoporosis. The administration of birth control pills in most cases has not been effective in reconstituting the skeleton. Both the caloric ratio and the exercise ratio have to be

adjusted if improvement is to be gained.

Work by Courtney et al⁴⁸ and Cummings et al⁴⁹ has demonstrated that fractures are very closely related to falls. A 1 SD decline in bone mass will increase the risk of hip fracture 2.5-fold, but trauma to the trochanter will increase the risk of fracture more than fivefold. Thus, programs that are directed at balance and fall prevention may be just as effective as medical manipulation of the skeleton and decrease the rate of falls.

It is recommended that individuals adopt all three components of an ideal exercise program—impact exercises, strengthening exercises, and balance training. The impact exercises are utilized to directly stimulate osteoblast formation and to ward off resorption. Exercises that meet these criteria include jogging, brisk walking, and stair climbing. Strengthening exercises will affect the bones underlying the exercised muscles. It is recommended that patients utilize light weights in a comprehensive program that strengthens the major axial and appendicular muscle groups. The patient should be alerted that doing sit-ups and lifting objects from a flexed position will increase the loads across the vertebral bodies and may surpass the ability of osteoporotic bone to tolerate such stresses. All exercises should be developed in terms of the potential of the individual and should progress from minimal loads to greater loads, giving sufficient time for the patient to accommodate to the program. Cross-training allows recovery from new injuries.

In light of the data from Cummings et al⁴⁹ and Courtney et al,⁴⁸ fall strategies are critical, including balance training. Simple exercises that meet these criteria include dancing and tai chi chuan. Individuals who practice tai chi have a 47% decrease in falls and one

fourth the hip fracture rate of those who do not. This discipline can be mastered by even the quite elderly population.⁵⁰

Summary

Osteoporosis is an ever-increasing problem as our population ages. It appears to affect men to the same degree as women (when data are corrected for age). All individuals should follow a program that includes adequate calcium replacement, 400 to 800 units of vitamin D, appropriate exercise, avoidance of significant weight loss, and cessation of smoking.

At menopause, women should evaluate their risk factors and consider the use of estrogen not only for its skeletal benefits but also for its nonosseous effects. A bone density evaluation may be helpful in this decision-making process, particularly if there are major risk factors, including low weight, history

of maternal fractures, history of individual fractures, and history of smoking. A bone density evaluation will determine only the current state of the skeleton, whereas assessment of collagen degradation peptide products will establish whether the patient's resorptive rate is high or relatively stable. If the bone mass is low (on the order of 2.0 to 2.5 SDs below normal peak bone mass) or if there is an increase in resorption and risk factors (particularly if there are fragility fractures), use of one of the three antiresorptive agents (estrogen, bisphosphonates, or calcitonin) may be appropriate. When these modes of therapy have failed or there is evidence of low-turnover osteoporosis with osteoblast formation failure, the soon-to-be-released slow-release sodium fluoride should be considered. Various bisphosphonates are being released in ever-increasing numbers, as well as a whole family of selective estrogen-receptor modulators, of which

raloxifene is now approved by the FDA. The latter has the benefits of estrogen and at the same time reduces the incidence of breast cancer.

Two thirds of the cost of osteoporosis in the United States is due to hip fractures. The orthopaedist is the primary physician who comes in contact with osteoporotic fragility fractures. It is his or her responsibility to become knowledgeable about the treatment and prevention of osteoporosis. The bisphosphonates, hormones, and calcitonin provide predictable restoration of bone mass and significantly diminish the rate of fragility fractures. In our institution, we have an active case-finding program among the fracture patients, and we follow them up aggressively to be sure they are adequately treated to prevent future fractures. Every orthopaedist who treats fractures is encouraged to initiate such a program.

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