JH is a 56-year-old postmenopausal woman who comes to your office prior to starting her new job as an accountant. She has several health concerns. Her 82-year-old mother was recently hospitalized with a broken hip. JH is 62 inches tall and weighs 114 pounds. She does not enjoy physical exercise. She smoked cigarettes for 25 years, but stopped smoking five years ago. She is concerned about osteoporosis, and wants to know whether she should be screened for osteoporosis, and what she could do to prevent herself from developing a hip fracture in the future. She rarely drinks alcohol and does not take any medication at the present time. In response to recent concerns about the detrimental effects of hormone replacement therapy (HRT), JH discontinued her use of this therapy 2 years ago.

Points to consider...

- What is osteoporosis?
- How can osteoporosis be prevented?
- How is osteoporosis diagnosed?
- What are the treatment options available for osteoporosis?
- What other therapeutic choices are available?
THE CLINICAL CRISIS

Osteoporosis affects an estimated 75 million people in Europe, the United States, and Japan.\(^1\) Fractures due to osteoporosis are a principal cause of disability and death. Approximately 1.5 million fragility fractures (fractures occurring after trauma no greater than a fall from a standing height) occur annually in the United States, and this number will increase as the “baby boomers” reach their 70s.\(^2\)\(^,\)\(^4\) Unfortunately, this number underestimates the true impact of bone disease, because it captures the problem at a point in time. The impact of bone disease is more appropriately evaluated over a lifetime. Four out of every 10 white women age 50 or older in the United States will experience a hip, spine, or wrist fracture sometime during the remainder of their lives; 13 percent of white men in this country will suffer similar fates.\(^19\) Further, fewer than one third of patients who have had osteoporotic-related fractures are appropriately evaluated and treated for osteoporosis.

Fractures can have devastating consequences for both the individuals who suffer them and their family members. For example, hip fractures are associated with increased risk of mortality. The risk of mortality is 2.8-4 times greater among hip fracture patients during the first 3 months after the fracture, as compared to the comparable risk among individuals of similar age who live in the community and do not suffer a fracture.\(^20\)

The financial burden of osteoporosis is quite significant as well. The direct care expenditures for osteoporotic fractures alone range from $12.2-$17.9 billion each year, measured in 2002 dollars.\(^2\) Adding in the direct costs of caring for other bone disease as well as the indirect costs (e.g., lost productivity for patients and family members) would likely add billions of additional dollars to this bill.

In 2004, the Surgeon General released a report on bone health and osteoporosis states that if without an increase in public awareness and prevention of osteoporosis, that it is estimated that in 2020 one in two Americans over age of 50 will have, or be at high risk of developing, osteoporosis.\(^2\) By 2010, roughly 12 million individuals over age 50 are expected to have osteoporosis and another 40 million to have low bone mass.\(^5\)

If these predictions come true, they will have a devastating impact on the well-being of Americans as they age. As part of its Healthy People 2010 initiative, the U.S. Department of Health and Human Services (HHS) has developed two overarching goals that are highly relevant to bone health and osteoporosis. The first goal is increased quality and years of
healthy life. The second goal is to eliminate health disparities across different segments of the population.²

**DEFINITION OF OSTEOPOROSIS**

In 1991, a consensus panel defined osteoporosis as “a loss of bone mass and microarchitectural deterioration of the skeleton leading to increased risk of fracture.”¹⁴ Since microarchitectural deterioration cannot be directly measured, the Working Group of the World Health Organization (WHO) has defined osteoporosis as a bone mineral density (T score) that is 2.5 SD below the mean peak value in young adults.⁶ They also suggested that osteopenia or low bone mass be applied when T scores are from -1.0 to -2.5.

**RISK FACTORS**

A number of risk factors for osteoporosis have been identified (Table 1).⁷ Bone loss can be slowed or even reversed if risk factors such as low dietary calcium intake, physical inactivity, and primary hyperparathyroidism are identified and reversed. A report from the National Osteoporosis Foundation concluded that the following factors were useful in identifying women at risk for fracture: low body weight (< 58 kg), current smoking, first-degree relative with low-trauma fracture, and personal history of low-trauma fracture.⁸

Table 1. Risk Factors for Osteoporosis in Postmenopausal Women. Genetic factor

<table>
<thead>
<tr>
<th>Genetic factor</th>
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<tbody>
<tr>
<td>• First-degree relative with low trauma fracture</td>
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<table>
<thead>
<tr>
<th>Environmental factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cigarette smoking</td>
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<tr>
<td>• Alcohol abuse</td>
</tr>
<tr>
<td>• Physical inactivity</td>
</tr>
<tr>
<td>• Thin habitus</td>
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<tr>
<td>• Diet low in calcium</td>
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<tr>
<td>• Little exposure to sunlight</td>
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<table>
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<tr>
<th>Menstrual status</th>
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<tbody>
<tr>
<td>• Early Menopause (before the age of 45 years)</td>
</tr>
<tr>
<td>• Previous amenorrhea (e.g., due to anorexia nervosa, hyperprolactinemia)</td>
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</table>
Estimates of relative risk associated with various factors differ among studies, but there is general consensus regarding the importance of several key factors in risk assessment. In postmenopausal white women, the relative risk of fracture is increased by a factor of 1.5 to 3 each decrease of 1.0 in the T score, depending on the site measured. The relative risk increases by a factor of 2 to 3 per decade after the age of 50. The most important risk factor for fracture, independent of bone mineral density, is a previous fragility fracture.

<table>
<thead>
<tr>
<th>Drug therapy</th>
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<tbody>
<tr>
<td>• Glucocorticoids (7.5mg/day or more of prednisone for more than 6 mo)</td>
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<tr>
<td>• Antiepileptic drugs (e.g., phenytoin)</td>
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<tr>
<td>• Excessive substitution therapy (e.g., thyrozine, hydrocortisone)</td>
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<tr>
<td>• Anticoagulant drugs (e.g., heparin, warfarin)</td>
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<tr>
<th>Endocrine diseases</th>
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<tbody>
<tr>
<td>• Primary hyperparathyroidism</td>
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<tr>
<td>• Thyrotoxicosis</td>
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<tr>
<td>• Cushing’s syndrome</td>
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<tr>
<td>• Addison’s disease</td>
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<tr>
<th>Hematologic diseases</th>
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<tbody>
<tr>
<td>• Multiple myeloma</td>
</tr>
<tr>
<td>• Systemic mastocytosis</td>
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<tr>
<td>• Lymphoma, leukemia</td>
</tr>
<tr>
<td>• Pernicious anemia</td>
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<table>
<thead>
<tr>
<th>Rheumatologic disease</th>
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<tbody>
<tr>
<td>• Rheumatoid arthritis</td>
</tr>
<tr>
<td>• Ankylosing spondylitis</td>
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<tr>
<th>Gastrointestinal diseases</th>
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<tbody>
<tr>
<td>• Malabsorption syndromes (e.g., celiac disease, Crohn’s disease, surgery for peptic ulcer)</td>
</tr>
<tr>
<td>• Chronic liver disease (e.g., primary biliary cirrhosis)</td>
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</table>
This history increases the risk of future fractures by as much as a factor of 8; the risk is highest in the first year or two after the initial episode.\(^9\)

Falls are another important predictor, especially for hip fracture in the elderly. Hence, factors that increase the risk of falling – such as impaired vision, neuromuscular deficits, or medications that affect balance – should also be assessed.\(^{13}\) Other risk factors should be assessed, although their relationship to bone density and fractures are less clear-cut. Low intake of alcohol (one to two drinks per day) is associated with increased bone mineral density, but higher intakes are associated with low bone mass and increased risk of fracture, perhaps related to falls.\(^{14}\) Low 25-hydroxyvitamin D levels (less than 20 mg per milliliter) increase the risk of fragility fractures; this is attributed not only to lower bone mineral density but also to a direct neuromuscular effect of vitamin D that may reduce the frequency of falls.\(^{15}\)

Patients with inflammatory disorders involving the musculoskeletal, gastrointestinal, or pulmonary system and patients who have chronic renal disease or have undergone organ transplantation are also at increased risk for low bone mineral density and fracture.\(^{14}\) Medications, particularly glucocorticoids, may be an aggravating factor. Neurologic diseases can cause bone loss due to immobilization and to the adverse effects of antiepileptic drugs on vitamin D homeostasis.\(^{14}\) Less common causes of low bone mass include congenital abnormalities such as osteogenesis imperfecta and homocystinuria, cancer involving the skeleton (particularly myeloma), and hyperplastic anemia.\(^{14}\)

**SCREENING**

Dual-Energy X-Ray Absorptiometry:

The current practice is to perform dual-energy x-ray absorptiometry (DEXA) of the lumbar vertebrae (L1 to L4); the hip, including the femoral neck, Ward’s triangle, the greater trochanter, and the total hip (which includes all these measures).\(^{14}\) Ward’s triangle is the area within the femoral neck in which trabeculae are normally thin and loosely arranged, and is enclosed by trabeculae from the principle compressive group, the second compressive group and the tensile group. The results of the test are presented visually, including both T scores and Z scores (the bone density in the patient as compared with other people of the same age and size expressed as the number of SDs above or below the mean). Of the hip measures, the femoral neck and total hip, in particular, are the most useful in predicting fracture, whereas measurements of Ward’s triangle show greater
variation and of little clinical value.\textsuperscript{14} Although it has been suggested that the WHO definition of osteoporosis should be reserved for patients with low T scores for the total hip, low T scores at other sites are also considered diagnostic of osteoporosis. Spinal measurements may be particularly important in younger postmenopausal women, since they may show osteoporotic values earlier than the hip.

The problem with spinal measurements in older women, however, is that sclerotic changes that occur with age, largely owing to osteoarthritis, may result in an artifactual increase in measured bone mineral density. Measurement of mineral density in forearm bone is not used routinely but is recommend for patients with primary hyperparathyroidism, since this site may show the greatest bone loss.\textsuperscript{16} Z scores are more informative than T scores in young persons, since the scoring allows comparison of bone density with persons of similar age, height, and weight. More generally, a Z score of -2.0 or lower is considered an indication of the need for more intensive evaluation of possible secondary causes of bone loss, although such causes should be considered in all cases.\textsuperscript{14}

Quantitative Computed Tomography:

Bone density can be measured by quantitative computed tomography (CT).\textsuperscript{14} This technique can analyze trabecular and cortical bone separately and is a sensitive measure of early bone loss in the vertebrae. However, the application of T scores to predict the risk of fracture with the use of quantitative CT has not been validated, and this technique is usually more costly and results in greater exposure to radiation than does DEXA.

Peripheral Measurements:

Because of the limited availability, lack of portability, and relatively high cost of DEXA, screening with the use of peripheral densitometry has been developed. These techniques include peripheral DEXA, x-ray absorptiometry, and ultrasonography of the radius, heel, and hands.\textsuperscript{14} The findings of decreased bone mineral density with these techniques predicts an elevated risk of fracture. However, the interpretation of T scores may not correspond to that of central DEXA measurements.\textsuperscript{17} Peripheral measurements should not be used for decision making in regard to diagnosis and management.
WHO SHOULD GET A DEXA SCAN?

The U.S. Preventive Services Task Force (USPSTF), the National Osteoporosis Foundation (NOF), and the American Association of Clinical Endocrinologists (AACE) have recommended that all women have a measurement of bone mineral density at the age of 65 years (in selected women, earlier).\textsuperscript{3, 21, 22} Strong indicators of the risk of future fracture are considered to be a basis for the recommendation of bone-mineral-density testing before the age of 65 years.\textsuperscript{14} A prior fragility fracture warrants bone mineral density testing not only among postmenopausal women but also among men and premenopausal women. A family history of fracture, low body weight, and a loss of either weight (5 percent of baseline weight or more) or height are additional indications,\textsuperscript{14} as are conditions or drugs known to be associated with bone loss, including primary hyperparathyroidism, hyperthyroidism, hypogonadism (due to disease or drugs), Cushing’s syndrome, and long-term glucocorticoid therapy. The USPSTF recommends that women who are 60 to 65 years old and have multiple risk factors undergo bone-mineral-density testing, whereas NOF and AACE suggest that any postmenopausal women with multiple risk factors should be tested. However, the guidelines do not specify how risk factors should be assessed or weighted. The International Society for Clinical Densitometry and AACE have provide additional guidelines for testing in men, premenopausal women, and children.\textsuperscript{21, 22} These guidelines recommend bone-mineral density testing in patients who have diseases or are receiving drugs that are likely to cause secondary osteoporosis (including glucocorticoids, antiepileptic drugs, luteinizing hormone-releasing hormone agonists, and aromatase inhibitors) and all patients with fragility fractures.

Laboratory Assessment

Laboratory assessment is not used to screen for the presence of osteoporosis but is routinely indicated in patients with low Z scores (for example, -2.0 SDs or below) and may be useful in other patients with low bone density, with the goal of identifying secondary causes (such as elevated serum calcium levels suggesting hyperparathyroidism) or factors that can aggravate bone fragility (such as low level of 25-hydroxyvitamin D) that can be treated.\textsuperscript{14} Clinical or laboratory evidence of disorders such as hyperthyroidism, glucocorticoid excess, gonadal dysfunction, gastrointestinal or renal disease, and cancer warrants appropriate testing. Patients with low bone mineral density and weight loss should be screened for celiac disease, even if they do not have gastrointestinal symptoms.\textsuperscript{18}
Biochemical markers of bone turnover reflect bone formation or bone resorption (Table 2). These markers show large changes early in the course of treatment. Due to the fact that the markers vary from day to day, several measurements should be made before and during treatment.

Table 2: Biochemical Markers of Bone Turnover

<table>
<thead>
<tr>
<th>Bone formation</th>
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<tr>
<td>• Serum alkaline phosphatase (bone isoenzyme)</td>
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<td>• Serum osteocalcin</td>
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<tr>
<td>• Serum C- and N-propeptides of type I collagen</td>
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<table>
<thead>
<tr>
<th>Bone resorption</th>
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<tbody>
<tr>
<td>• Urinary excretion of pyridinium cross-links of collagen (e.g., deoxypyridinoline)</td>
</tr>
<tr>
<td>• Urinary excretion of C- and N-propeptides of collagen</td>
</tr>
<tr>
<td>• Urinary excretion of galactosyl hydroxylysine</td>
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<tr>
<td>• Urinary excretion of hydroxyproline</td>
</tr>
<tr>
<td>• Serum tartrate-resistant acid phosphatase</td>
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**PATHOPHYSIOLOGY OF OSTEOPOROSIS**

Bone mineral density in a patient is related to bone mass at maturity (peak bone mass) and subsequent bone loss. Bone is remodeled throughout life, and the rate of remodeling is increased in older adults. The rate of resorption exceeds the rate of formation in older adults, resulting in too little bone, or osteoporosis. The process of resorption of bone, followed by synthesis of bone matrix and its subsequent mineralization, takes up to eight months. If the process of bone resorption and bone formation is not matched, there is remodeling imbalance. Such an imbalance would be magnified if the rate of initiation of new cycles of bone remodeling were to increase.

Most of the drugs used to treat osteoporosis act by decreasing bone resorption and are referred to as antiresorptive drugs. They include estrogens, bisphosphonates, and calcitonin. The name is misleading: because the processes of bone resorption and bone formation are coupled, these drugs decrease the rates of both processes. Consequently, antiresorptive drugs decrease the rate of initiation of new remodeling cycles, resulting in fewer remodeling sites and a decrease in the remodeling space. The bone mineral density
of postmenopausal women given antiresorptive therapy often increase 5 to 10 percent after two to three years of therapy, but then changes very little afterwards.

Some drugs used to treat osteoporosis work by increasing bone formation. They include fluoride and intermittent parathyroid hormone. Drugs that stimulate bone formation result in annual rates of increase in bone mineral density similar to those resulting from antiresorptive therapies, but the increase continues beyond two years.

Hormones and drugs affect different regions of the skeleton by differing amounts. These differences may be due to different effects on cortical and cancellous bone, on bones subjected to weight-bearing and those subjected to non-weight-bearing stresses, or on bones containing red marrow and those containing yellow marrow. For example, estrogen deficiency and glucocorticoid therapy results in primarily in cancellous-bone loss, whereas parathyroid hormone excess results primarily in cortical-bone loss.

**TREATMENT**

Calcium and Vitamin D:

Elderly women adapt poorly to a low-calcium diet, and those who live at far northern or southern latitudes or who avoid sunlight may become deficient in Vitamin D. In a study of 3270 institutionalized women in France who were treated with calcium (1200 mg per day) and vitamin D (800 IU per day) for three years, the risk of hip fractures was 30 percent lower than the risk in the placebo group. This therapy also resulted in a reversal of secondary hyperparathyroidism and an increase in the bone mineral density of the femoral neck. In a more recent study of 389 men and women over the age of 63 years who were treated with calcium (500 mg per day) and vitamin D (700 IU per day) in the United States, the rate of nonvertebral fractures was decreased. This decrease was surprising since the increases in bone mineral density of lumbar spine (0.9 percent), femoral neck (1.2 percent) and total body (1.2 percent) were small. The key differences in these two studies were the lower base-line dietary intake of calcium and the higher serum 25-hydroxyvitamin D concentrations in the U.S. patients.

Calcium alone may be partially effective in preventing bone loss, especially in older women and those with a low calcium intake. In a study of 86 women treated with 1000 mg of calcium per day or placebo for four years, there was a sustained reduction in the loss of total-body bone mineral density in the calcium group; there was also a reduction in the loss
of lumbar-spine and proximal-femur bone mineral density, with most of the difference occurring during the first year of calcium supplementation. There was a borderline reduction in the rate of symptomatic fractures in the calcium group as compared with the placebo group.

The active metabolite of vitamin D, calcitriol, and the related alfacalcidol (1α-hydroxvitamin D) increase calcium absorption, may have direct effects on bone cells and may reduce the rate of fracture. Vitamin D is a fat soluble vitamin that is found in food (e.g. fortified milk, egg yolks, saltwater fish, liver and supplements) and can also be made in your body after exposure to ultraviolet (UV) rays from the sun. Sunshine is a significant source of vitamin D because UV rays from sunlight trigger vitamin D synthesis in the skin. The liver and kidney help convert vitamin D to its active hormone form. Once vitamin D is produced in the skin or consumed in food, it requires chemical conversion in the liver and kidney to form 1,25 dihydroxyvitamin D, the physiologically active form of vitamin D. Active vitamin D functions as a hormone because it sends a message to the intestines to increase the absorption of calcium and phosphorus.

The National Osteoporosis Foundation recommends that adults under age 50 need 1,000 mg of calcium daily, and adults age 50 and over need 1,200 mg of calcium daily. Further, they recommend that adults under age 50 need 400-800 IU of vitamin D₃ daily, and adults age 50 and older need 800 – 1,000 IU of vitamin D₃ daily. Vitamin D₃ is the form of vitamin D that best supports bone health. It is also called cholecalciferol.

Calcitonin:
Calcitonin is a 32-amino-acid peptide that is normally produced by the thyroid C cells and results in decreased bone resorption. Osteoclasts have calcitonin receptors, and calcitonin rapidly inhibits the action of osteoclasts.

Salmon or human calcitonin is given by subcutaneous or intramuscular injection at doses up to 100 IU daily. Calcitonin therapy results in an increase in bone mineral density, and in one unblinded study it resulted in a decrease in the rate of vertebral fracture. It is expensive, must be given by injection, and can cause nausea, flushing, and diarrhea. Some patients become resistant to its actions with long-term use. The development of intranasal salmon calcitonin may make calcitonin therapy more acceptable. At least 200 IU per day must be given to have an effect on bone mineral density and is not effective in preventing bone loss in early postmenopausal women. In older women it decreased the vertebral-
fracture rate, but the number of fractures was small. The spray has few side effects (nasal discomfort, nausea, and facial flushing) and, like subcutaneous calcitonin, it has an analgesic effect.\(^7\)

**Bisphosphonates:**

Bisphosphonates are stable analogues of pyrophosphate. They are poorly absorbed from the intestine (absorption, less than 10 percent)\(^7\) and must not be taken with food. They are deposited in bone at sites of mineralization and in the resorption lacunae or are eliminated by the kidneys. The exact mode of action is uncertain, but their net effect is on osteoclasts or their precursors, with a resultant increase in cell death and therefore a decrease in bone resorption.\(^27\) Bisphosphonate therapy results in increased bone mineral density and a decreased fracture rate.

Etidronate given continuously at high doses can result in impaired mineralization, which can be avoided by low-dose intermittent therapy.\(^7\) The drug is usually given at a dose of 400 mg per day for 2 weeks, followed by 500 mg of supplemental calcium per day for 11 weeks. This regimen resulted in an increase in bone mineral density of 4 to 8 percent in the lumbar spine and of 2 percent in the femoral neck in three years, as well as a decrease in the vertebral-fracture rate.\(^7, 28\)

Alendronate is given at a dose of 10 mg per day for treatment of osteoporosis in postmenopausal women. Alendronate resulted in an increase in bone mineral density of 8.8 percent in the lumbar spine and of 5.9 percent in the femoral neck in three years.\(^29\) The report also showed that alendronate therapy also resulted in a 48 percent decrease in the proportion of women with new fractures and prevented height loss. In another report from a two-year prevention study, 5 mg of alendronate per day had less effect on bone mineral density than estrogen-replacement therapy but resulted in fewer adverse events.\(^30\)

Among the 2027 women with vertebral fractures in the Fracture Intervention Trial\(^31\) who were treated with 5 mg of alendronate daily for two years, with a subsequent increase to 10 mg per day for the final nine months of the study, the rate of new vertebral fractures (including those that were apparent clinically) decreased by 47 percent as compared with the rate in the placebo group. There were similar decreases in the frequency of hip and wrist fractures but not of other fractures.
Alendronate has been associated with esophagitis including erosive esophagitis. The symptoms of esophagitis usually begin within one month after therapy is started. To minimize the risk of esophagitis and increase in drug absorption, the patient should take alendronate with a glass of water while upright at least 30 minutes before breakfast. Upper gastrointestinal problems, such as achalasia and esophageal stricture, are absolute contraindications to alendronate therapy, and gastroesophageal reflux disease is a relative contraindication.

Bone turnover increases to the previous level in six to nine months in women who take alendronate for six months and then stops. In contrast, among women treated with pamidronate for six years, bone mineral density did not decrease during the first two years after therapy was discontinued. The optimal duration of bisphosphonates therapy is not known.

Fluoride:

Sodium fluoride stimulates bone formation by unknown mechanisms. In one study of 202 women with osteoporosis who were treated with sodium fluoride, lumbar-spine bone mineral density increased by 8 percent per year during all four years of the trial. There was substantial bone loss from the forearm, indicating redistribution of bone mineral from the cortical to cancellous bone. The Fluoride and Vertebral Osteoporosis Study was a randomized, placebo-controlled, two-year trial of sodium fluoride (50 mg per day) and monofluorophosphate (two doses) in 354 women with osteoporosis. Fluoride therapy, as compared with placebo, had a large effect on bone mineral density in the lumbar spine (increase, 10.8 percent vs. 2.4 percent), but no effect on the rate of vertebral fracture. Thus, even at relatively low doses, fluoride had little beneficial effect on fracture rates. Sodium fluoride causes gastric irritation, which can be reduced if the drug is given along with a calcium supplement. It also causes stress fractures.

Estrogen-Replacement Therapy:

Taking estrogen brings a woman's estrogen levels back to premenopausal levels. This slows bone thinning and causes some increase in bone thickness. Progestin works like the naturally occurring hormone progesterone and prevents endometrial cancer from developing in women who have a uterus.
The Women's Health Initiative (WHI) study showed that hormone replacement therapy (HRT) can lower the risk of osteoporosis-related hip fractures and other fractures in postmenopausal women. But taking HRT led to small increases in the number of women who developed breast cancer, ovarian cancer, heart attack, stroke, blood clots (pulmonary embolism and deep vein thrombosis), and Alzheimer's disease and other dementias. Most experts recommend that HRT should only be considered for women with a significant risk of osteoporosis that outweighs the risks of taking HRT.

**FUTURE TREATMENTS**

**Raloxifene:**

Raloxifene has mixed estrogen-agonists and estrogen-antagonist activity and is referred to as a selective estrogen-receptor modulator (SERM). In a two-year study in postmenopausal women, raloxifene therapy resulted in a decrease in bone resorption and an increase in bone mineral density in the lumbar spine (2.4 percent), total hip (2.4 percent), and total body (2.0 percent). In a randomized placebo-controlled trial (Raloxifene Use for The Heart [RUTH] trial), 10,101 postmenopausal women 55 years of age or older who had or were at increased risk for coronary heart disease were either given oral raloxifene 60 mg per day or a placebo over approximately 5 years. The raloxifene and placebo groups did not differ for the composite endpoint of coronary events or for any of the component outcomes individually. Raloxifene reduced risk for invasive breast cancer — in particular, estrogen-receptor-positive breast cancer; it did not prevent estrogen-receptor-negative or noninvasive breast cancer. Groups did not differ for stroke, but risks for fatal stroke and VTE were increased in the raloxifene group. Raloxifene reduced clinical vertebral fractures but not nonvertebral fractures. Groups did not differ for death from cardiovascular causes or death from all causes. Hot flashes, leg cramps, peripheral edema, and gallbladder disease were reported by more women in the raloxifene group. Groups did not differ for endometrial cancer. As with any other medication, each individual postmenopausal woman’s risk/benefit ratio must be carefully considered.

**Parathyroid Hormone:**

Parathyroid hormone (PTH) is one of the two major hormones modulating calcium and phosphate homeostasis, the other being calcitriol (1,25-dihydroxyvitamin D). With respect to calcium, PTH is most responsible for maintaining serum ionized calcium concentrations within a narrow range, through its actions to stimulate renal tubular calcium reabsorption and bone resorption. Chronic exposure to high serum PTH concentrations (as seen with
primary or secondary hyperparathyroidism) results in bone resorption. Given this observation, exogenous, parathyroid hormone (PTH) seems an unlikely candidate for the treatment of osteoporosis. However, intermittent administration of recombinant human PTH (both full-length 1-84 and fragment 1-34) stimulates bone formation more than resorption.

Daily injections of parathyroid hormone stimulate bone formation. It may be given as the intact hormone or as synthetic fragment. PTH treatment for at least 18 months markedly reduces the risk of spine fractures in postmenopausal women with osteoporosis. The risk reduction becomes apparent after eight months of treatment, and the effect is not dose dependent nor does it depend upon the type of PTH.

Some common side effects of PTH treatment include hypercalcemia and hypercalciuria. PTH should not be used in individuals with renal stones or persistent hypercalciuria. Occasional hypotension or tachycardia can occur with the first few doses. Nausea and headache are reported among individuals treated with PTH but these do not appear to be significantly different from placebo. Debilitating muscle cramps have also been reported following PTH treatment as well. Very few long-term side effects have been reported with PTH. Some investigators have reported improvement in back pain with PTH therapy, but it is unclear whether this is a function of fewer fractures, or a true analgesic response. The most worrisome adverse events is the development of osteosarcoma. Of 300,000 patients worldwide treated with Forteo (PTH 1-34, teriparatide), there has been one reported case of osteosarcoma in a postmenopausal women taking Forteo. Causality between Forteo and the osteosarcoma could not be established in this patient. Currently, the FDA contends that PTH therapy be limited to two years, pending further post-marketing studies. Given its cost, subcutaneous route of administration, long-term safety concerns, and availability of other agents, PTH is generally not used as a first-line drug for treatment or prevention of osteoporosis.

Other Therapies:

A number of cytokines and growth factors have potent effects on bone cells. These factors also affect other organs; for example, cytokines modulate the immune system. The challenge will be to target such factors to bone. Other drugs that have been developed for the treatment of osteoporosis include vitamin D analogues, strontium salts (S12911), and ipriflavone.
THERAPEUTIC CHOICES

The women who are most at risk for fractures should be treated. Women with osteoporosis often present with acute vertebral fracture. During the acute phase, the pain can usually be managed with analgesic drugs and a lumbar-support corset. If this is ineffective, a short period of bed rest and calcitonin therapy (for its analgesic properties) should be tried.

Lifestyle changes should be recommended, including the avoidance of heavy lifting and the encouragement of exercise, such as walking. Falls can be prevented by exercise and the avoidance of sedating drugs. Although hip protectors can protect against hip fractures for frail elderly women, compliance is poor given it bulky nature. Calcium intake should be increased to 1500 mg per day, and if the patient is vitamin D deficient, then they should be repleted appropriately. Further, excess consumption of alcohol should be avoided, and tobacco eliminated.

It is important to select the appropriate treatment for each woman. Often, bisphosphonates are appropriate first choice treatments. The importance of the timing of administration should be stressed, and the response to treatments should be monitored.

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