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Focus on Women's Health:
The Prevention and Treatment of Osteoporosis

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LEARNING OBJECTIVES

1. Discuss the clinical presentation of osteoporosis.
2. Discuss the presence of risk factors in special populations presenting with the disease.
3. Discuss the role of hormone replacement therapy and calcium supplementation in the prevention and treatment of the disease.
4. Differentiate between the various classes of drugs used to treat osteoporosis, including common side effects and contraindications.
5. Compare and contrast teriparatide, a new drug recently approved to treat osteoporosis, with older, more established agents.

ABSTRACT: In recent years, Women's Health issues have gained much attention in the medical community. For many years, diseases that seemed to have been specific to females were somewhat neglected or not focused upon by physicians. No longer is this the case. A disease such as osteoporosis, once thought to only affect elderly Caucasian women, is now being given much attention.

The broken hip experienced by a 70-year-old female as a result of brittle bones and a subsequent fall was not thought about at age 20, when she could have started on the road to prevention. Women must be educated about a disease that might be prevented simply by taking precautionary measures such as proper diet, adequate exercise, and calcium supplementation. Women should also be informed that new medications are available that can be used to both treat and prevent this disease.

While estrogen maintains a Food and Drug Administration (FDA)-approved indication for the prevention of osteoporosis, recent results of the estrogen plus progestin trial (EPT) of the Women's Health Initiative (WHI) make continued use of the drug somewhat controversial. The FDA revised estrogen-containing product labels to read, "*When these products are being prescribed solely for the prevention of postmenopausal osteoporosis, approved non-estrogen treatments should be carefully considered, and combination estrogen therapy should only be considered for women with significant risk of osteoporosis that outweighs the risks of the drug*." Two medications in the bisphosphonate class, alendronate and risedronate, have garnered a significant portion of the pharmacy market share and have been proven to be very effective in both the prevention and treatment of this disease. Though these drugs have been associated with severe gastrointestinal side effects if not administered properly, patient counseling by a pharmacist as to proper use can alleviate any such occurrence. Raloxifene and calcitonin are other medications used to treat and/or prevent the disease. The newest

medication indicated for treatment of osteoporosis is teriparatide. Teriparatide was released onto the market in November 2002, and is a recombinant form of parathyroid hormone (PTH). Reserved for patients who are considered high risk, and unlike other drugs used to treat osteoporosis, which are antiresorptive, this drug is classified as a bone formation agent.

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FOCUS ON WOMEN'S HEALTH: THE PREVENTION AND TREATMENT OF OSTEOPOROSIS

INTRODUCTION

Many women do not think much about osteoporosis until it's too late. The broken hip experienced by a 70-year-old female as a result of brittle bones and a subsequent fall was not thought about at age 20, when she could have started on the road to prevention. Women should be educated about a disease that might be prevented just by taking precautionary measures such as diet, exercise, and supplementing calcium. Women should also be informed that new medications are available that can be used to both treat and prevent this disease. This article will discuss the prevalence and incidence of the disease, pathophysiology, risk factors, diagnosis, special populations, and both the prescription and nonprescription medications used for prevention and treatment.

The National Osteoporosis Foundation defines osteoporosis as a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures.[1] These fractures most commonly involve the patient's hip, spine, or wrist. In terms of prevalence, osteoporosis is a major public health concern affecting an estimated 44 million Americans. Of this 44 million, it is estimated that 10 million have the disease while the remaining, or 34 million, are osteopenic (those having low bone mass that increases their risk for osteoporosis and may eventually lead to the disease).[1, 2] In terms of gender, of the 10 million Americans that have the disease, 8 million are women and 2 million are men. Because of a population that is aging and that Americans are living longer, osteoporosis is becoming more prevalent and more expensive. Current estimates indicate that the annual cost associated with the disease is $14 billion dollars. [1, 2]

Patients at increased risk include females, particularly those patients who are postmenopausal; those with a family history; small framed individuals; those who experienced the onset of menses at a later age; those who experienced menopause at an earlier age; those of Caucasian or Asian descent (more prevalent in the former than the latter); and smokers. Though not as prevalent, increased risk has also been reported in other ethnic groups such as African-Americans and Hispanics, and is thought to occur in patients of advanced age.

When women reach perimenopause, the decrease in estrogen levels lead to an increased risk for osteoporosis.[3]

Risk factors for osteoporosis are both nonmodifiable and potentially modifiable. Non-modifiable risk factors, or those risk factors over which the patient has no control, include advanced age, dementia, female sex, family history, and race. Modifiable risk factors include alcohol use, smoking, estrogen deficiency, testosterone deficiency, inadequate dietary calcium, inadequate exercise, or low body weight. Patients should be encouraged to make every effort to improve as many modifiable risk factors as possible.[1, 2, 4]

There are 2 types of osteoporosis: primary and secondary. The diagnosis of primary osteoporosis is made after all other possible illnesses, diseases, and drugs have been excluded. There are 2 types of primary osteoporosis: Type I, or postmenopausal osteoporosis, affects women after menopause and is associated with wrist and vertebral fractures. Bone resorption increases in the absence of estrogen decreasing overall bone mass and increasing fracture risk. Type II, referred to as age-related or senile osteoporosis, affects men and women over the age of 70 and is associated with hip and vertebral wedge fractures. Secondary osteoporosis, which is not related to age or gender, is associated with other illnesses (e.g., endocrine disorders, gastrointestinal (GI) disease, and oncologic diseases) or the use of medications, the most common of which are glucocorticoids, although excess thyroid hormone and anticonvulsant therapy are also known causes.[2, 4]

The consequences of osteoporosis are varied; however, hip fractures account for a significant portion of osteoporosis-related mortality with 12%-36% of patients dying within one year of the fracture.[1, 2] Other consequences include a loss of up to 6 inches in height, otherwise known as the characteristic dowager's hump, chronic and/or acute back pain, GI, or respiratory distress.

PATHOPHYSIOLOGY

Human bone undergoes a constant regeneration process with both osteoclasts (bone-resorbing cells) and osteoblasts (bone-forming cells) usually present in somewhat equal proportions.[5, 6] It is when this proportion becomes unbalanced that the disease osteoporosis presents. Bone strength is also dependent upon the structural characteristics of the skeleton (i.e., shape and size).[7]

The underlying cause of the disease may be attributable to either an increase in osteoclasts or a decrease in osteoblasts resulting in low bone mineral density (BMD). The former may occur following a decrease in estrogen owing to menopause and the latter as a result of the normal aging process.

DIAGNOSIS

For the first time, the U.S. Preventive Services Task Force has recommended that women aged 65 and older be routinely screened for osteoporosis to reduce the risk of fracture and spinal abnormalities often associated with the disease. The Task Force also recommends that routine screening begin at age 60 for those women identified as high risk because of low weight or lack of estrogen use.[8]

To make a definitive diagnosis, BMD testing must be performed. Bone mass or density is defined as the amount of mineral (calcium) contained within a specific amount of bone and is usually expressed in

grams per square centimeter of the area scanned.[9]

The World Health Organization (WHO) has developed diagnostic criteria for both osteopenia and osteoporosis. The BMD for a healthy patient is defined as a value within 1 standard deviation (SD) of young adult mean or T-score above -1. (T-score is defined as the patient's bone mass compared with the mean peak bone mass of a normal young adult, sex-adjusted reference population). A patient is considered osteopenic when the BMD value is between 1 SD and 2.5 SDs below the mean, T-score between -1 and -2.5. A diagnosis of osteoporosis is made when the BMD value is at least 2.5 SDs below the mean, T- score below -2.5. A patient is considered to have severe osteoporosis when the BMD value is -2.5 SDs or more with the presence of a fracture. Though not as relevant but similar in concept to the T-score, Z-scores are sometimes used, using the mean BMD and SD for a healthy, age-matched population as reference values.[9, 10]

The most accurate method of diagnosing osteoporosis in postmenopausal women is made with the dual energy x-ray absorptiometry, commonly referred to as DEXA. There are 3 types of BMD measurement: 1) the full-body DEXA, 2) the portable DEXA, and 3) the quantitative ultrasound. The full-body DEXA is considered the gold standard in the diagnosis of osteoporosis because of its high accuracy and low radiation exposure. Performed on an outpatient basis, this method not only measures the total body, but also measures spine, hip, and forearm as well, exposing the patient to a small amount of radiation. This method can be costly if not covered by patient insurance. The second method, portable DEXA or pDXA, measures the BMD at peripheral sites such as the heel and forearm. This method is an alternative to and is less expensive than the full-body DEXA. The third method, the quantitative ultrasound, is the newest form of measurement and predicts fracture risk at a relatively low cost and without exposure to potentially harmful radiation. Prospective studies using this method have predicted fractures almost as well as the DEXA.

SPECIAL POPULATIONS

African-Americans

A common misconception is that African-American women are at significantly lower risk for osteoporosis attributable to increased body mass index and bone density. As all women age, the risk of fractures also increases; therefore, this would also indicate that the risk of fractures for all races would increase. Many African-American women do not believe that they are prone to the development of osteoporosis and tend to be somewhat resistant to the use of any type of medication to either prevent or treat the disease. Studies have shown that the decrease in fracture incidence among black women may be because of 3 factors: higher peak bone mass at skeletal maturity; age-related bone loss may begin at a later age, be less severe, or occur in different skeletal sites; or bone mass and rate of loss may be similar in both groups, but other risk factors, such as frequency of falls, may differ.[12,13,14] One study suggests that higher tracebular bone density in African-American girls does exist but only becomes apparent during puberty.[12]

Further studies provided data indicating that age-specific incidence rates for hip fracture in African-American women are about half that of Caucasian women, but are still considerable. It is also important to note that the impact of hip fracture is particularly devastating to African-American females,

which attributes to higher rates of morbidity and mortality.[13]

African-American women are also believed to have lower levels of serum 25-hydroxy vitamin D $25(OH)D_3$ levels and higher levels of parathyroid hormone (PTH) than Caucasian women because of reduced absorption of sunlight through their skin. The correction of secondary hyperparathyroidism has been shown to be useful in reducing bone loss in elderly white women. A study performed with 10 healthy postmenopausal black women who received 20 mcg of vitamin D_3 daily for 3 months showed that the mean serum $25(OH)D_3$ levels increased by more than twice its value at the beginning of the study. The study concluded that supplementation with vitamin D_3 raises serum $25(OH)D_3$ levels, decreases secondary hyperparathyroidism, and reduces bone turnover, but that further study with larger patient populations inclusive of more data would be needed.[15]

Another issue facing this population is one of lactose intolerance. According to the National Institutes of Health (NIH), approximately 75% of all African-Americans are lactose intolerant.[4] Since the ingestion of dairy products has been shown to cause GI intolerance manifesting as flatulence and stomach upset, calcium may need to be supplemented with special formulations of orange juice or mineral water that contain it.

Men

According to the National Osteoporosis Foundation, 2 million men in the U.S. have osteoporosis and 12 million more are at risk. During the physical examination, the health care provider may overlook osteoporosis in men. The following risk factors are associated with osteoporosis in this population: prolonged exposure to medications such as glucocorticoids, chronic disease affecting major organs, undiagnosed low levels of testosterone, smoking, excessive alcohol use, low calcium intake, inadequate exercise, age, heredity, and race. As in women, bone loss in men increases with age. With regard to race, white men are at greatest risk, but men from all ethnic groups may develop the disease.[16]

Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS)

Estimates indicate that 38.6 million adults worldwide are living with the human immunodeficiency virus, more commonly referred to as HIV. Of this number, approximately 50% or 19.2 million are women. The estimated number of AIDS diagnoses in the U.S. through 2002 is said to be in excess of 850,000 people. Of this number, approximately 160,000 are women, the largest growing segment of the population being of African-American ethnicity.[17]

With continued advances in treatment, patients currently diagnosed with HIV/AIDS are living longer, healthier lives, attributable, in large part to the use of powerful drugs, referred to as highly active antiretroviral therapy (HAART). Patients treated with these medications may, however, suffer metabolic complications such as lipodystrophy, insulin resistance, diabetes, dyslipidemia, and alterations in BMD as a result.

The first decrease in BMD in the HIV population was reported approximately 6 years ago.[18] The cause of low BMD in this group is unknown, although it has been attributed to several factors. The HIV virus is said to do the following:

1) Have a direct effect on the osteogenic cells
2) Activate tumor necrosis factor-alpha
3) Alter the metabolism of vitamin D
4) Impact the various opportunistic infections found in these patients
5) Have mitochondrial abnormalities related to lactic acidosis

The decreases in BMD were originally attributed to the use of drugs in the protease inhibitor class such as indinavir, nelfinavir, saquinavir, and the newest agent in the class, fosamprenavir, released in October 2003. This theory, however, has not been proven.

In a study involving 142 subjects, both male and female, the BMD in HIV-positive patients was significantly lower when compared with controls. (This result was independent of drug therapy.) The study concluded that any decrease in BMD was associated with the length of time of the infection rather than the drug therapy used, which suggests that the virus itself does have an independent negative effect on bone metabolism.[18, 19]

Renal Impairment

Because osteoporosis is a disease that is more prevalent in the older patient population, and a major group of drugs is used to both prevent and treat the disease (bisphosphonates) are excreted by the kidneys, knowledge of a patient's renal function is of paramount importance prior to patients using bisphosphonates. Though the relevance is clear, most clinical studies involving these drugs have excluded females with renal compromise.

In an effort to study the occurrence of renal compromise in patients with osteopenia and osteoporosis, researchers used data from the Third National Health and Nutrition Examination Survey, 1988-1994 (NHANES III). The parameters of serum creatinine (normal value SCr = 0.6 to 1.2) and creatinine clearance (normal value CrCl = 70-110 ml/min) were used in the study. The results indicated that mild-to-moderate renal compromise (CrCl < 60-70 ml/min) was estimated to be present in 85% of women with osteoporosis who were between the ages 20-80+ and severe renal compromise (CrCl < 35ml/min) to be present in 24% of this population. The conclusion was therefore reached that there is a significant number of female patients with either osteopenia or osteoporosis who are also renally impaired. This finding should alert the medical community as to the necessity of possible dosage adjustments.[20] The manufacturers of alendronate and risedronate do not recommend a dosage adjustment in patients whose creatinine clearance is within the range of 35-60 ml/min; however, it should be noted that the use of their products is not recommended in patients whose creatinine clearance is below 35 ml/min.[21, 22] Clinical studies with raloxifene in patients with renal impairment have not revealed any differences in the concentration in patients with creatinine clearance as low as 23 ml/min and controls with normal renal function.[23]

PREVENTION

Osteoporosis can be prevented by non-pharmacologic methods such as diet, exercise, calcium supplementation, or pharmacologic methods such as the use of prescription medications. Medications known to cause an increased risk of falls include antihypertensives such as diuretics and vasodilators, analgesics prescribed for pain relief such as nonsteroidal anti-inflammatory drugs (NSAIDs), sedatives such as long-acting benzodiazepines prescribed for insomnia or anxiety, and psychotropic drugs that affect cognition or

balance. Because of this, a thorough medication profile review should be performed and unnecessary medications identified and discontinued.

Fall prevention should also be practiced in the elderly patient.[2] Pharmacists, in addition to providing medication counseling, should also counsel patients and/or caregivers to improve lighting; clear hallways and stairways of any clutter; avoid the use of throw rugs without rubber-backing; and encourage patients to use canes, walkers and supportive shoes whenever necessary.

External hip protectors have also been used in some elderly patients reducing hip fractures by about 60%; however, compliance is very poor owing to discomfort.[2] Recent evidence has also shown that there may be little or no benefit to their use.

PHARMACOLOGIC TREATMENT

Patients who have been diagnosed with osteoporosis may be prescribed one of the following medications to treat the disease. Current medications include calcium, the bisphosphonates, selective estrogen receptor modulators (SERMs), calcitonin, and parathyroid hormone (PTH).

Nonprescription, Over-the-Counter (OTC) Medications

Calcium is the most abundant mineral in the body. While it is best to meet the recommended daily allowance through the consumption of dairy products such as milk, cheese, and yogurt; fish; and vegetables such as mustard greens and broccoli, many patients are unable to take in adequate amounts in their diets.[22] Calcium should play a major role in the promotion of good bone health beginning early in childhood. It is important to note that intestinal absorption of calcium does decrease by approximately 50% during the aging process. This is of particular importance to the postmenopausal woman.

Because the majority of calcium is present in the skeleton of the body, it is a major component of bone. Calcium has many functions, some of which include activating enzymes required for the synthesis of acetylcholine (ACh), aiding in the absorption of vitamin B_{12}, and regulating muscle contraction and relaxation.

The NIH recommended daily allowance of calcium for the average adult is 1000 mg per day. For postmenopausal women, this amount should be increased to 1500 mg per day.

Commercially available nonprescription calcium products are available for those patients who may be lacking adequate amounts of calcium in their diet and are in need of supplementation. These products contain one of many salt forms: carbonate, citrate, lactate, or gluconate; each product differs in the amount of elemental calcium contained. Calcium carbonate, the most widely used, provides the largest amount of elemental calcium by weight (40%) followed by phosphate salt (30%-37.5%), citrate salt (21%), lactate salt (18%), and gluconate salt (9%). Another advantage of products containing carbonate salt is the low cost. Disadvantages, however, include differences in bioavailability, erratic absorption, and constipation. Administration of these tablets with food has been shown to eliminate or further resolve some of these issues.

Calcium citrate is excellent as alternative therapy when patients are unable to tolerate products containing the carbonate salt form. Calcium citrate tablets provide 200 to 315 mg of elemental calcium with greater

absorption and may be taken with or without food, but are more expensive and are available in fewer product formulations. Since an acidic environment is not required for maximum absorption as is the case with the carbonate salt, this form is beneficial for patients suffering from GI problems such as achlorhydria (the absence of hydrochloric acid in the stomach) and those taking proton-pump inhibitors or H_2 receptor antagonists.

It is neither recommended nor beneficial for patients to exceed greater than 2500 mg daily doses of calcium because of the risk of hypercalcemia and hypercalciuria. Adverse effects of the drug include cramps, constipation, bloating, and gas.

Calcium absorption may be decreased by fiber and antacids and may decrease the absorption of flouroquinolones, iron, and tetracyclines resulting in drug interactions, which may render these medications less therapeutically effective. The role of vitamin D in enhancing the intestinal absorption of calcium has been well documented. Most patients require a daily dose of 400 IU, but it is recommended that this amount should be increased to 800 IU in elderly patients suffering from severe osteoporosis; the maximum daily dose should not exceed 1200 IU per day.

Prescription Medications

Estrogen

The use of hormone replacement therapy for prevention or treatment of either menopause or osteoporosis has been of particular controversy over the past year and a half owing to the findings of the estrogen plus progestin trial (EPT) of the Women's Health Initiative (WHI) in the summer of 2002. The EPT involved 16,608 women with an intact uterus ranging in age from 50 to 79 years old. The participants were randomized to receive a daily dose of 0.625 mg conjugated equine estrogens (CEE) and 2.5 mg of medroxyprogesterone or placebo. In May 2002, a review of the trial data showed a 26% increase in the number of cases of invasive breast cancer in this group; a finding that resulted in the abrupt discontinuation of the trial. The study also showed a 41% increase in strokes, a 29% increase in heart attacks, a doubling of the rates of venous thromboembolism (VTE) (blood clots), and a 22% increase in total cardiovascular disease. Surprisingly, the trial showed a 37% reduction in colorectal cancer risk.[24]

In relation to osteoporosis, the specific finding for the estrogen plus progestin therapy group when compared with placebo included a one-third reduction in hip fracture rates and a 24% reduction in total fractures. Various clinical trials continue to test preventive measures for heart disease, breast and colorectal cancer, and osteoporosis.[25] Even though estrogen maintains a FDA-approved indication for the prevention of osteoporosis, recent results of the EPT make continued use of the drug somewhat controversial. The FDA revised estrogen-containing product labels in January 2003 to read, "*When these products are being prescribed solely for the prevention of postmenopausal osteoporosis, approved non-estrogen treatments should be carefully considered, and combination estrogen therapy should only be considered for women with significant risk of osteoporosis that outweighs the risks of the drug*."[26]

It is recommended that doses of CEE lower than 0.625 mg be prescribed and taken in combination with calcium and vitamin D supplementation. Lower doses reportedly result in fewer episodes of uterine bleeding and breast tenderness.[2] Ethinyl estradiol and

transdermal 17-β estradiol are other forms that may be used.

Bisphosphonates

Bisphosphonates are currently the drugs of choice used for both the prevention and treatment of osteoporosis.[27] Older drugs in this class used to treat Paget's disease did not have a FDA-approved indication for osteoporosis. The newer agents, alendronate and risedronate, are more potent, more selective, and inhibit bone resorption at concentrations lower than those that alter bone histology.[6]

Bisphosphonates are synthetic analogues of naturally occurring inorganic pyrophosphates that bind tightly to hydroxyapatite crystals in bone matrix. These agents are specific for bone because of their high binding affinity for calcium phosphates. Alendronate and risedronate are classified as third-generation agents. Previous generations include first-generation etidronate and second-generation pamidronate, clodronate, and tiludronate. The third-generation agents are more selective owing to their inhibition of bone resorption at lower concentrations and are more than 500 times more potent than their first-generation counterpart etidronate.[6]

Poorly absorbed from the GI tract because of extremely low bioavailability when administered on an empty stomach, absorption of these agents is further reduced when taken with food or chelating agents like iron or calcium-containing compounds.[5,6] Once in the bloodstream, up to 50% of the drug binds to the bone surface. The unabsorbed fraction is excreted unchanged in the urine. Though the bisphosphonates have a short half-life, they are present in the bone for long periods of time.[5]

Bisphosphonates are not metabolized and undergo renal excretion within 12 hours of administration. Caution must be exercised in patients with renal insufficiency because of the possibility of accumulation and resulting adverse effects. Clinical trials examining the use of these drugs have been limited mainly to patients with normal renal function; therefore, administration should be avoided in patients whose creatinine clearance is less than 30-35ml/min and until such time that more information is available.[5]

As a class, the bisphosphonates are generally well tolerated if taken as directed. The most common adverse event involves gastrointestinal disturbances such as heartburn, esophagitis, and esophageal irritation. Other events include muscle pain and headache. Most of these side effects may be avoided by proper administration of the drug. It is recommended that the drugs be taken with 6 to 8 ounces of plain water at least 30 minutes prior to the first food, drink, or medication of the day. The patient should also remain upright for at least 30 minutes and until after the first food of the day, a process that aids in the delivery of the drug to the stomach. The drugs are contraindicated in patients with any abnormality of the esophagus or anyone suffering from hypocalcemia. Any patient who is unable or unwilling to closely follow the administration guidelines would also not be a good candidate for bisphosphonate therapy.[28, 29]

Alendronate was the first of the 2 third-generation bisphosphonates developed for treatment of osteoporosis, which was approved for use by the FDA, following several clinical trials that demonstrated its efficacy. One of the landmark trials to study the drug was the Fracture Intervention Trial (FIT) involving 2,027 postmenopausal

women with pre-existing vertebral fractures. Two groups were randomized to receive either alendronate 5 mg/day for the first 2 years, followed by 10 mg/day for the third year, or placebo. The alendronate group showed a 51% reduction in hip fractures, a 47% reduction in wrist fractures, and a 47% reduction in new vertebral fractures. The study showed a significant increase in BMD at the femoral neck, total hip, and lumbar spine compared with placebo.[30]

Manufactured by Merck & Co., under the trade name Fosamax®, the drug is available in 5-, 10-, and 40-mg (daily) tablet formulations; in 35- and 70-mg (weekly) tablet formulations; and in an oral solution. It is indicated for the prevention and treatment of osteoporosis in postmenopausal women, for increasing bone mass in men with osteoporosis, for the treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low BMD, and for the treatment of Paget's disease of the bone in men and women. Weekly dosing has been shown to be as effective as daily dosing, and is believed to be better tolerated.[29, 31]

To evaluate the efficacy of the drug in men, a 2-year trial involving 241 men with a history of fracture or low hip BMD were randomized to receive either alendronate 10 mg/day or placebo. At the end of the 2-year study period, the lumbar spine BMD increased by 7.1% in the alendronate group and 1.8% in the placebo, femoral neck BMD increased 2.5% in the alendronate group and decreased 0.1% in the placebo group, and new vertebral fractures occurred in 0.8% of those on alendronate, compared with 7.1% in the placebo group. The authors concluded that the benefits of alendronate therapy in men with the disease were similar to those seen in postmenopausal women.[5]

Risedronate, the second of the third-generation bisphosphonates developed and approved for the treatment and prevention of osteoporosis in postmenopausal women, is also indicated for the prevention and treatment of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoid treatment and for Paget's disease of the bone.[22, 29] Manufactured by Procter and Gamble under the trade name Actonel®, the drug is available in both 5- and 30-mg daily and 35-mg weekly formulations. The Vertebral Efficacy with Risedronate Therapy (VERT) Trial, the landmark trial for risedronate, involved 2,458 postmenopausal women with pre-existing vertebral fractures randomized to receive risedronate 2.5 mg or 5 mg/day or placebo for 3 years. The risedronate 5-mg/day group showed a 41% reduction in vertebral fractures and 39% reduction in nonvertebral fractures. Compared with placebo, treatment with risedronate increased BMD significantly at the lumbar spine and femoral neck.[5]

In clinical trials comparing risedronate with alendronate, non-placebo–controlled comparisons indicate that risedronate appears to have fewer adverse effects on the GI tract than does alendronate; however, placebo-controlled comparisons do not exhibit any difference between the two.[29]

Selective Estrogen Receptor Modulators (SERMs)

SERMs have both agonist and antagonist properties depending upon the tissue site involved. Raloxifene, a second-generation selective estrogen receptor modulator (SERM), is indicated for use in the prevention and treatment of osteoporosis in

postmenopausal women. As a result of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, it was determined that raloxifene significantly increased BMD and reduced the risk of fracture in women with osteoporosis. The trial included 7,705 postmenopausal women with osteoporosis or with one or more vertebral fractures who received raloxifene 60 mg per day for 3 years or placebo. At the end of the trial, both the lumbar spine and femoral neck BMD were higher in the raloxifene group than in the placebo group. Both results were found to be statistically significant. The risk of nonvertebral fractures was similar in both groups.[21]

Raloxifene exhibits both agonist and antagonist effects: agonist effects on bone and cholesterol metabolism and antagonist effects on the breast and the uterus. Manufactured by Eli Lilly and Company under the trade name Evista®, the drug is available as a 60-mg tablet. Raloxifene is classified as a second-generation SERM, while tamoxifen, also in the same class, is a first-generation SERM that has partial agonist activity in the uterus. (Clomiphene, a medication indicated for ovulation induction in the treatment of infertility, is also considered a SERM.)[21] The drug is rapidly absorbed from the GI tract, undergoes extensive first-pass metabolism, is widely distributed in the tissues, and is excreted in the feces. The most common side effects found in the MORE clinical trial, resulting in the withdrawal of 1.2% of study participants in the raloxifene group, were hot flushes and leg cramps. Raloxifene has also been shown to increase the risk of VTE, and should be used with caution in women at risk for thromboembolic disease.[2, 21] Women in the raloxifene group of the MORE trial had 3 times as many cases of VTE as placebo recipients.[21]

Though shown to increase BMD in clinical trials, raloxifene has been proven less effective than both estrogen and the bisphosphonates. The drug does, however, have positive effects on markers of cardiovascular risks, and is a viable alternative for women who cannot tolerate the side effects of estrogen therapy. Another benefit reported with use of the drug includes a decrease in new cases of breast cancer.[28]

Calcitonin

Calcitonin, a polypeptide derived from salmon, is FDA approved for use in the treatment of osteoporosis in women who are more than 5 years' postmenopause. Calcitonin is indicated for treatment of Paget's disease of the bone and as adjunctive therapy in hypercalcemia, but has only been approved for the treatment of osteoporosis and not for prevention. The drug has also been shown to have an analgesic effect in patients with acute fracture pain or skeletal metastases. Available in 2 forms, injection and nasal spray, the mechanism of action of the drug involves a decrease in bone resorption by inhibition of osteoclast function. The drug also promotes the renal excretion of calcium, phosphate, sodium, magnesium, and potassium by decreasing tubular reabsorption.[2, 22, 28]

The dosage for the injection manufactured under the trade name Calcimar® is 100 units per day administered intramuscularly or subcutaneously. The dosage for the intranasal spray manufactured under the trade name Miacalcin® is 200 units or one spray daily. Side effects of the drug include facial flushing, nausea, diarrhea, and specifically for the injection, edema at the injection site.[32]

Teriparatide

Teriparatide, a recombinant form of PTH, was approved for use by the FDA in November 2002, and is manufactured by Eli Lilly and Company under the trade name Forteo®. Unlike the other drugs used to treat osteoporosis, it is classified as a bone formation agent and not as an antiresportive agent. Forteo® is indicated to treat postmenopausal women who are at high risk for fractures and to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fractures. The drug is not indicated as first-line therapy but is reserved for those cases in which patients have proven resistant to other agents (e.g., bisphosphonates).[33]

The main function of PTH is the regulation of calcium and phosphate in the kidney. It is responsible for regulation of bone metabolism, tubular reabsorption of calcium and phosphate, and intestinal absorption of calcium. Stimulation of the PTH receptor in bone results in the formation of osteoclasts.[33]

A randomized, double-blind, placebo-controlled, 2-year trial involving 1,637 women with osteoporosis resulted in the following conclusion: teriparatide combined with daily amounts of calcium and vitamin D increased bone density and reduced fracture incidence in amounts that were statistically significant.[33]

Following a single, daily, subcutaneous injection of 20 mcg into the thigh or abdomen, teriparatide is absorbed very rapidly and extensively. The drug labeling contains a "black box warning" concerning the risk/possibility of the development of an osteosarcoma (found in animal models studied). Because of this finding, the drug should not be used in children who are still growing or those with Paget's disease, or patients known to be at increased risk for the development of cancers. The adverse effects of the drug include nausea, dizziness, hypercalcemia, leg cramps, and it has also been shown to increase serum uric acid concentrations. No clinically important adverse effects have been reported in regard to renal function; however, there have been isolated reports of an increase in serum creatinine and alkaline phosphatase levels and a decrease in magnesium levels. The values have been shown to return to normal following a 5-week period. Teriparatide is contraindicated for use in patients with hypercalcemia, those who are pregnant or nursing, and those with a history of cancer of any type. [33, 34]

Recent studies have also found that bisphosphonates may interfere with bone effects of PTH. No additive effect has been realized when the 2 drugs have been used in combination therapy. In a 12-month study, 238 postmenopausal women with low BMD at the hip or spine took either PTH or alendronate or both. An increase in BMD occurred in all treatment groups with none being statistically significant. In fact, the study showed that a greater increase in BMD was realized in patients receiving PTH alone rather than in combination. Similar results were obtained from another study involving 83 men with low BMD.[35]

It has been determined that a "washout/waiting" period is not necessary for patients found to be in need of PTH following failure of bisphosphonate therapy. Because bisphosphonates remain on the surface of the bone and in the skeleton for many years, they may be discontinued and teraparatide therapy begun immediately.

A manufacturer-implemented risk management program has been initiated, and includes comprehensive educational

measures regarding the appropriate use of teriparatide in the target population. The FDA recommends that teriparatide not be used for a period longer than 2 years.[34, 35]

Table I: FDA-Approved Pharmacologic Treatment

Generic Name	Trade Name	Indication	Dosages	Dosage Forms	Side Effects
Estrogens	Various	Prevention of osteoporosis	Equivalent to 0.3-0.625 mg po daily	Tablet, Vaginal cream, Injection	Bloating, breast tenderness, uterine bleeding
Bisphosphonates					
Alendronate	Fosamax®	Prevention and treatment of osteoporosis; Paget's disease	Prevention: 5 mg po daily, 35 mg po weekly Treatment: 10 mg po daily, 70 mg po weekly	Tablet, Oral solution	Heartburn, esophageal irritation, esophagitis, abdominal pain, diarrhea
Risedronate	Actonel®	Prevention and treatment of osteoporosis; Paget's disease	Prevention: 5 mg po daily, 35 mg po weekly	Tablet	
Selective Estrogen Receptor Modulators					
Raloxifene	Evista®	Prevention and treatment of osteoporosis	60 mg po daily	Tablet	Hot flushes, leg cramps, venous thromboembolism
Calcitonin	Miacalcin®	Treatment of osteoporosis	100 IU SC or IM qod, 200 IU intranasally	Injection, Nasal spray	Nausea, flushing
Parathyroid Hormone					
Teriparatide	Forteo®	Treatment of osteoporosis in high-risk women and men	20 mcg SC daily	3 ml pre-filled pen delivery device	Nausea, headache, dizziness, leg cramps

ALTERNATIVE THERAPIES

None of the currently available alternative therapies have been proven efficacious in either the prevention or treatment of osteoporosis. Soy food is shown to have little or no benefit to the skeleton when ingested in regular amounts. Likewise, in preliminary studies, ipriflavone was shown to reduce bone loss but failed to improve BMD or reduce fracture.[26] The American College of Obstetricians and Gynecologists (ACOG) recognizes the role of phytoestrogens contained in black cohosh, ginseng, and licorice, but the use of these products beyond a 6-month time period is not supported.

CONCLUSION

There is evidence of a growing incidence of osteoporosis in both the U.S. and the world. This fact is particularly true in this country owing to the increasing number of female baby boomers approaching menopause. Studies have proven that the decline of estrogen in the postmenopausal female may lead to osteoporosis, a disease that may be prevented with proper diet, weight-bearing exercise, smoking cessation, calcium supplementation, and medication. Though most prevalent in women, the disease is also present in men.

There are several treatment options for patients subsequently diagnosed with the disease. Because of the findings of the EPT of the WHI, long-term use of estrogen replacement therapy is not recommended. While not approved for the treatment of osteoporosis, the drug does have a FDA-approved indication for prevention. The EPT showed an increase in strokes, heart attacks, blood clots, and cardiovascular disease but demonstrated favorable results in the form of reductions in colorectal cancer risk and both hip and total fracture rates.

Alendronate and risedronate, both bisphosphonates, are the most commonly used drugs for both the prevention and treatment of osteoporosis today. Patients unable to tolerate these drugs because of GI side effects may be prescribed raloxifene, a SERM, though it has been shown to be weaker than the bisphosphonates. Calcitonin may be recommended for those women who are 5 years' postmenopause. For patients suffering from severe osteoporosis or treatment failure with bisphosphonate therapy, teriparatide or PTH is available for use but not for longer than a 2-year period. To date, there are no proven herbal or alternative therapies for prevention or treatment of the disease.

Regardless of the chosen treatment, calcium and vitamin D are essential to bone growth and strength; they remain a mainstay of therapy and should be included in every regimen.

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