Osteoporosis

Drug Approvals

- In 2008, the Food and Drug Administration (FDA) approved a generic version of the osteoporosis drug alendronate (Fosamax).
- In 2008, the FDA broadened the use of once-yearly zoledronic acid (Reclast) to include the prevention of new fractures in patients who have had previously had a hip fracture. Reclast was previously approved as the first once-yearly injectable drug for treatment of postmenopausal osteoporosis.
- In 2008, the FDA approved a new once-a-month dose of risedronate (Actonel).

Osteoporosis Screening

Bone density testing is recommended for:

- All women over age 65
- Postmenopausal women under age 65 with one or more risk factors for osteoporosis
- All men over age 70
- Men ages 50 - 70 with one or more risk factors for osteoporosis.
- Any man or women over age 50 who has suffered a fracture.
- People with specific risk factors for osteoporosis. These risk factors include long-term use of medications such as corticosteroids, history of certain medical conditions (diabetes, thyroid imbalances), history of breast or prostate cancer treatment, significant loss of height or recent weight loss.

Osteoporosis Risk Factors

- Age is the main risk factor for osteoporosis. Aging causes bones to thin and weaken. Although osteoporosis affects mostly postmenopausal women, older men are also at risk.
- Osteoporosis is more common in people who have a small, thin body frame and bone structure.
- Dietary calcium and vitamin D deficiencies are important factors in the risk for osteoporosis.
- Women who smoke, particularly after menopause, have a significantly greater risk of spine and hip fractures than those who do not smoke. Men who smoke also have lower bone density.

Introduction

Osteoporosis is a skeletal disease in which bones become brittle and prone to fracture. In other words, the bone loses density. Osteoporosis is diagnosed when bone density has decreased to the point where fractures occur with mild stress.

The skeleton consists of groups of bones which protect and move the body.

Until a healthy adult is around age 40, the process of breaking down and building up bone by cells called osteoclasts and osteoblasts is a nearly perfectly coupled system, with one phase balancing the other. As a person ages, or in the presence of certain conditions, this system breaks down and the two processes become out of sync. The reasons why this occurs during aging are not clear, but declining levels of sex hormone are one factor. Some individuals have a very high turnover rate of bone, some have a very gradual turnover, but the breakdown of bone eventually overtakes the build-up.

The Bones

The Function of Bones. The skeleton has a dual function:

- It provides structural support for muscles and organs.
- It also serves as a depot for the body's calcium and other essential minerals, such as phosphorus and magnesium.

The skeleton holds 99% of the body's calcium. The remaining 1% circulates in the blood and is essential for crucial bodily functions, ranging from muscle contraction to nerve function to blood clotting.

Bone Turnover: the Breakdown and Growth of Bones. Like other organs in the body, bone tissue is constantly being broken down and reformed again. This turnover is necessary for growth, for repair of minor damage that occurs from everyday stress, and for the maintenance of a properly functioning body. Two essential cells are involved in this process:

- Osteoclast cells are formed from certain blood cells and are responsible for the breakdown, or *resorption*, of the skeleton. These cells dig holes into the bone and release the small amounts of calcium into the bloodstream that are necessary for other vital functions.
- Osteoblast cells are produced by bone cells and are the bone builders. They rebuild the skeleton, first by filling in the holes with collagen, and then by laying down crystals of calcium and phosphorus.

Each year, about 10 - 30% of the adult skeleton is remodeled in this way. The balance of bone build-up (formation) and break down (resorption) is controlled by a complex mix of hormones and chemical factors. If bone resorption occurs at a greater rate than bone build up, your bone loses density and puts you at risk for osteoporosis.

In women, estrogen loss after menopause is associated with rapid resorption and loss of bone density. This group, then, is at highest risk for osteoporosis and therefore for fracture.

Primary Osteoporosis

There are two primary kinds of osteoporosis:

- High-turnover osteoporosis (sometimes called type I) occurs in 5 - 20% of women, most often between the ages of 50 and 75. This is because of the sudden postmenopausal decrease in estrogen levels, which results in a rapid depletion of calcium from the skeleton. This is associated with fractures that occur when the vertebrae compress together, causing a compression of the spine. It is also associated with fractures of the hip, wrist, or forearm caused by falls or minor accidents. Women have a higher risk for type 1 osteoporosis than men.
- Low-turnover osteoporosis (also known as age-related or senile osteoporosis or type II) results when the process of resorption and formation of bone are no longer coordinated, and bone breakdown overcomes bone building. (This occurs with age in everyone to some degree.) Type II osteoporosis affects both men and women and is primarily associated with leg and spinal fractures. Older women can have both type I and type II osteoporosis.

What determines the existence of osteoporosis, of either type, is the amount of calcium left in the skeleton and whether it places a person at risk for fracture. Someone who has exceptionally dense bones to begin with will probably never lose enough calcium to reach the point where osteoporosis occurs, whereas a person who has low bone density could easily develop osteoporosis despite losing only a relatively small amount of calcium.

Secondary Osteoporosis

Secondary osteoporosis is caused by other conditions, such as hormonal imbalances, diseases, or medications (such as corticosteroids or anti-seizure drugs).

Causes

Because the patterns of reforming and resorbing bone often vary from patient to patient, doctors believe several different factors account for this problem. Important chemicals (such as estrogen, testosterone, parathyroid hormone, and vitamin D) and blood factors that affect cell growth are involved with this process. Changes in levels of any of these factors can play a role in the development of osteoporosis.

The Role of Sex Hormones in Bone Breakdown

Although normally associated with women, sex hormones play a role in osteoporosis in both genders, most likely by controlling the birth and duration of life of both osteoclasts (bone breakers) and osteoblasts (bone builders).

Women and Estrogen. A woman experiences a rapid decline in bone density after menopause, when her ovaries stop producing estrogen. Estrogen comes in several forms:

The uterus is a hollow muscular organ located in the female pelvis between the bladder and rectum. The ovaries produce the eggs that travel through the fallopian tubes. Once the egg has left the ovary it can be fertilized and implant itself in the lining of the uterus. The main function of the uterus is to nourish the developing fetus prior to birth.

- The most potent form of estrogen is estradiol. Estradiol deficiency appears to be a very strong factor in the development of osteoporosis.
- The other important but less powerful estrogens are estrone and estriol.

The ovaries produce most of the estrogen in the body, but it can also be formed in other tissues, such as the adrenal glands, body fat, skin, and muscle. After menopause, some amounts of estrogen continue to be manufactured in the adrenals and in peripheral body fat. Even though the adrenals and ovaries have stopped producing estrogens directly, they continue to be a source of the male hormone testosterone, which converts into estradiol.

Estrogen may have an impact on bone density in various ways, including preventing bone breakdown (resorption).

Men and Androgens and Estrogen. In men, the most important androgen (male hormone) is testosterone, which is produced in the testes. Other androgens are produced in the adrenal glands. Androgens are converted to estrogen in various parts of a man's body, including bone.

Studies have suggested that the loss of estrogen as well as testosterone may contribute to bone loss in elderly men. Both hormones appeared to be integral to bone function in men.

Vitamin D and Parathyroid Hormone Imbalances

Low levels of vitamin D and high levels of parathyroid hormone (PTH) are associated with hip fracture in women after menopause:

- Vitamin D is a vitamin with hormone-like properties. It is essential for the absorption of calcium from the intestines and for normal bone growth. Lower levels result in impaired calcium absorption, which in turn causes an increase in PTH.
- Parathyroid hormone (PTH) is produced by the parathyroid glands. These are four small glands located on the surface of the thyroid gland. They are the most important regulators of calcium levels in the blood. When calcium levels are low, the glands secrete more PTH, which then increases blood calcium levels. High persistent levels of PTH stimulate bone resorption (bone loss).

Genetic Factors

Several studies on family members, including twins, have strongly suggested that genetic factors help determine bone density.

Causes of Secondary Osteoporosis

Corticosteroids. More than 30 million Americans use corticosteroid drugs (also called glucocorticoids or steroids) to treat disorders. Oral corticosteroids can reduce bone mass in both men and women. It is not clear whether inhaled steroids carry the same risks, but some studies indicate that they may cause bone loss when taken at higher doses for long periods of time. (Children on inhaled steroids may have temporary impaired growth, but they do not appear to be at risk for bone loss.)

Diuretics. Diuretics, which are used to treat high blood pressure, have different effects on osteoporosis, depending on the type. Loop diuretics, such as furosemide (Lasix), increase the kidneys' excretion of calcium, which can lead to thinning bones. Thiazide diuretics, on the other hand, protect against bone loss, but this protective effect ends after use is discontinued.

Contraceptives. Hormonal contraceptives that use progestin without estrogen (such as Depo-Provera injection or other progestin-based contraceptives), can cause loss of bone density. For this reason, the Food and Drug Administration (FDA) recommends that Depo-Provera injections should not be used for longer than 2 years. Some studies suggest that combination estrogen-progestin oral contraceptives increase the risk for osteoporosis later in life. Women who take birth control pills should be sure to get adequate calcium and vitamin D from diet or supplements.

Other Medications. Anti-epileptic (anti-seizure) drugs increase the risk for bone loss (as does epilepsy itself). Other drugs that increase the risk for bone loss include the blood-thinning drug heparin, and hormonal drugs that suppress estrogen (such as gonadotropin-releasing hormone agonists and aromatase inhibitors). Proton pump inhibitors (PPIs), which are used to treat gastroesophageal reflux disease (heartburn), may also increase the risk for bone loss and hip fractures. These drugs include omeprazole (Prilosec), lansoprazole (Prevacid), and esomeprazole (Nexium).

Medical Conditions. Osteoporosis can be secondary to several other conditions, including alcoholism, diabetes, hyperthyroidism, epilepsy, chronic liver or kidney disease, Crohn's disease, celiac disease, scurvy, rheumatoid arthritis, leukemia, cirrhosis, gastrointestinal diseases, vitamin D deficiency, lymphoma, hyperparathyroidism, and rare genetic disorders such as Marfan and Ehlers-Danlos syndrome.

Symptoms

Many people confuse osteoporosis with arthritis and believe they can wait for symptoms such as swelling and joint pain to occur before seeing a doctor. However, the mechanisms that cause arthritis are entirely different from those in osteoporosis. Osteoporosis usually becomes quite advanced before symptoms appear.

All too often, osteoporosis becomes apparent in dramatic fashion: A fracture of a vertebra (backbone), hip, forearm, or any bony site if sufficient bone mass is lost. These fractures

frequently occur after apparently minor trauma, such as bending over, lifting, jumping, or falling from the standing position.

Pain, disfigurement, and debilitation are common in the latter stages of the disease. Early spinal compression fractures may go undetected for a long time, but after a large percentage of calcium has been lost, the vertebrae in the spine start to collapse, gradually causing a stooped posture called *kyphosis,* or a "dowager's hump." Although this is usually painless, patients may lose as much as 6 inches in height.

Complications

Bone density loss from osteoporosis is a major cause of disability and death in the elderly, mostly due to subsequent fractures. The lifetime risk of spinal fracture in women is about one in three, and that for hip fracture is one in six. Women at highest risk for fractures are those with low bone density plus a history of fractures, particularly nonviolent fractures.

Osteoporosis causes more than 1.5 million fractures annually. About 50% of women and 25% of men over age 50 will suffer an osteoporosis-related fracture during their lifetime. Each year, there are about 700,000 spinal fractures, 300,000 hip fractures, 250,000 broken wrists and more than 300,000 fractures of other bones. About 80% of these fractures occur after relatively minor falls or accidents.

Unfortunately, studies continue to report inadequate treatment after a fracture. Few patients with sustained fractures are tested or treated for osteoporosis.

Risk Factors for Fracture and Falling. In addition to low bone density, falling is the primary risk factor for fractures. Additional risk factors for fracture are those that increase the risk for falling. They include:

- Having chronic medical problems (emphysema, heart disease, stroke, arthritis, and depression), with the risk increasing with multiple health problems
- Taking multiple medications (especially tranquilizers and antidepressants)
- Poor physical function, importantly slow gait and reduced muscle strength. Inactivity that results in weak thigh muscles and poor balance particularly puts any older person at risk for fracture and particularly those with low bone density.
- Poor concentration or mental impairment
- Impaired vision
- Hazardous environment (such as the presence of throw rugs in the house)

Mortality after Fracture

Hip fractures can increase the risk of death in both men and women. Complications of hip fractures include hospital-acquired infections and blood clots in the lungs.

Risk Factors

Gender

About 10 million adults in the United States have osteoporosis and another 34 million have low bone mass that places them at risk for developing osteoporosis. According to a report from the Surgeon General's office, by 2020 half of all Americans over age 50 could be at risk for this condition. Seventy percent of people with osteoporosis are women. Men start with higher bone density and lose calcium at a slower rate than women, which is why their risk is lower. Nevertheless, older men are also at risk for osteoporosis.

Age

As people age, their risks for osteoporosis increase. Aging causes bones to thin and weaken.

Ethnicity

Although adults from all ethnic groups are susceptible to developing osteoporosis, Caucasian and Asian women and men face a comparatively greater risk.

Body Type

Osteoporosis is more common in people who have a small, thin body frame and bone structure.

Family History

People whose parents had a history of fractures may be more likely to have fractures.

Hormonal Deficiencies

Women. Events associated with estrogen deficiencies are the primary risk factors for osteoporosis in women. These include:

- Menopause. Within 5 years after menopause, the risk for fracture increases dramatically. Fractures occurring during this period are more likely to occur in the wrist or spine than the hip, but their occurrence is a strong predictor of later severe osteoporosis and hip fracture.
- Surgical removal of ovaries
- Missing periods for 3 months or longer
- Never having given birth
- Anorexia nervosa, (an eating disorder), or extreme low body weight can affect the body’s production of estrogen

Men. Low levels of testosterone increase osteoporosis risk. Certain types of medical conditions (hypogonadism) and treatments (prostate cancer androgen deprivation) can cause testosterone deficiency.

Lifestyle Factors

Dietary Factors. Diet plays an important role in preventing and speeding up bone loss in men and women. Calcium and vitamin D deficiencies are important factors in the risk for osteoporosis. Other dietary factors may also be harmful or protective for certain people.

Calcium requires adequate vitamin D in order to be absorbed by the body. In the United States, many food sources of calcium such as milk are fortified with vitamin D.

Exercise. Lack of exercise and a sedentary lifestyle increases the risk for osteoporosis. Conversely, in competitive female athletes, excessive exercise may reduce estrogen levels, causing bone loss. (The eating disorder anorexia nervosa can have a similar effect.)

Lack of Sunlight. The photochemical effect of sunlight on the skin is a primary source for vitamin D. Bone formation peaks in the summer and bone breakdown increases in the winter. People who avoid sun exposure to prevent skin cancer may be at risk for vitamin D deficiency, particularly if they are elderly.

Smoking. Women who smoke, particularly after menopause, have a significantly greater chance of spine and hip fractures than those who don't smoke. Men who smoke also have lower bone density.

Alcohol. Excessive consumption of alcoholic beverages can increase the risk for bone loss.

Risk Factors in Children and Adolescents

The maximum density that bones achieve during the growing years is a major factor in whether a person goes on to develop osteoporosis. Persons, usually women, who *never* develop peak bone mass in early life are at high risk for osteoporosis later on. Children at risk for low peak bone mass include children who are:

- Born prematurely
- Have anorexia nervosa
- Have delayed puberty or abnormal absence of menstrual periods

Although to a large extent genetics predict bone health, exercise and good nutrition during the first three decades of life (when peak bone mass is reached) are still excellent safeguards against osteoporosis (and countless other health problems).

Diagnosis

Candidates for Bone Density Testing

Because osteoporosis can occur with few symptoms, testing is important. Bone density testing is recommended for:

- All women over age 65
- Postmenopausal women under age 65 with one or more risk factors for osteoporosis
- All men over age 70
- Men ages 50 - 70 with one or more risk factors for osteoporosis
- Any man or woman over age 50 who has suffered a fracture

Risk factors that may indicate a need for bone mineral density testing include:

- Long-term use of medications associated with low bone mass or bone loss such as corticosteroids, some anti-seizure medications, Depo-Provera, thyroid hormone, or aromatase inhibitors. Long-term use of glucocorticoids (more than 5 mg/day for more than 3 months) is a specific risk factor.
- History of treatment for prostate cancer or breast cancer
- History of medical conditions such as diabetes, thyroid imbalances, estrogen or testosterone deficiencies, early menopause, anorexia nervosa, rheumatoid arthritis
- Significant loss of height
- Significant recent weight loss or low body mass index

Tests Used for Measuring Bone Density

Central DXA. The standard technique for determining bone density is a form of bone densitometry called dual-energy x-ray absorptiometry (DXA). DXA is simple and painless and takes 2 - 4 minutes. The machine measures bone density by detecting the extent to which bones absorb photons that are generated by very low-level x-rays. (Photons are atomic particles with no charge.) Measurements of bone mineral density are generally given as the average concentrations of calcium in areas that are scanned.

A bone density scan measures the density of bone in a person. The lower the density of a bone the higher the risk of fractures. A bone scan, along with a patient's medical history, is a useful aid in evaluating the probability of a fracture and whether any preventative treatment is needed. A bone density scan has the advantage of being painless and exposing the patient to only a small amount of radiation.

Bone mineral density is usually measured at the hip and spine.

Other Tests. Other tests may be used, but they are not usually as accurate as DXA. They include ultrasound techniques and quantitative computed tomography (QCT) scan.

Screening tests using these technologies are sometimes given at health fairs or other non-medical settings. These screening tests typically measure peripheral bone density in the heels, fingers, or leg bones. The results of these tests may vary from DXA measurements of spine and hip. While these peripheral tests may help indicate who requires further BMD testing, a central DXA test is best for diagnosing osteoporosis and monitoring treatment response.

Diagnosing Osteoporosis and Predicting the Risk for Fracture

Osteoporosis is diagnosed when bone density has decreased to the point where fractures will happen with mild stress, the so-called fracture threshold. This is determined by measuring bone density and comparing the results with the norm, which is defined as the average bone mineral density in the hipbones of a healthy 30-year-old adult.

The doctor then uses this comparison to determine the standard deviation (SD) from this norm. Standard deviation results are given as Z and T scores:

- A T score gives the standard deviation of the patient in relationship to the norm in young adults. Doctors often use the T-score and other risk factors to determine the risk for fracture.
- A Z score gives the standard deviation of the patient in relationship to the norm in the patient's own age group and body size. Z scores may be used to for diagnosing osteoporosis in younger men and women. They are not normally used for postmenopaual women or for men age 50 and older.

Results of T-scores indicate:

- Between +1 and -1 indicates normal bone density.
- Between -1 and -2.5 indicates low bone density (osteopenia).
- A score of -2.5 or lower indicates a diagnosis of osteoporosis.

The lower the T-score, the lower the bone density, and the greater the risk for fracture. In general, doctors recommend beginning medication when T-scores are -2.5 or below. Patients who have other risk factors may need to begin medication when they have osteopenia (scores between -1 and -2.5).

Laboratory Tests

In certain cases, your doctor may recommend that you have a blood test to measure your vitamin D levels. A standard test measures 25-hydroxyvitamin D, also called 25(OH)D. Depending on the results, your doctor may recommend you take vitamin D2 supplements.

Lifestyle Changes

Healthy lifestyle habits, including adequate intake of calcium and vitamin D, are important for preventing osteoporosis and are also a useful accompaniment to medical treatment.

Calcium and Vitamin D

A combination of calcium and vitamin D can reduce the risk of osteoporosis. (For strong bones, people need enough of both calcium and vitamin D.) The National Osteoporosis Foundation (NOF) recommends:

- Adults under age 50 should have 1,000 mg of calcium and 400 - 800 IU of vitamin D daily.
- Adults age 50 and older should have 1,200 mg of calcium and 800 - 1,000 IU of vitamin D daily.

Dietary Sources. Good dietary sources of calcium include:

- Milk, yogurt, and other dairy products
- Dark green vegetables such as collard greens, kale, and broccoli
- Sardines and salmon with bones
- Calcium-fortified foods and beverages such as cereals, orange juice, soymilk

Certain types of foods can interfere with calcium absorption. These include foods high in oxalate (such as spinach and beet greens) or phytate (peas, pinto beans, navy beans, wheat bran). Diets high in animal protein, sodium, or caffeine may also interfere with calcium absorption.

Dietary sources of vitamin D include:

- Fatty fish such as salmon, mackerel, and tuna
- Egg yolks
- Liver
- Vitamin D-fortified milk, orange juice, soymilk, or cereals

However, many Americans do not get the vitamin D they need from diet or exposure to sunlight.

Supplements. Adults who consume adequate amounts of calcium through dietary sources may not need to take a supplement. Many require vitamin D, particularly if they do not get enough exposure to sunlight. Vitamin D is made in the skin using energy from the ultra-violet rays in sunlight. Because sun exposure increases the risk for skin cancer and premature skin aging, many Americans restrict their sunlight exposure. People's vitamin D levels decline as they age.

Calcium and vitamin D supplements can be taken as separate supplements or as a combination supplement. If taken separately, the supplements do not need to be taken at the same time.

- Calcium supplements include calcium carbonate (Caltrate, Os-Cal, Tums), calcium citrate (Citracal), calcium gluconate, and calcium lactate. Although each kind provides calcium, they all have different calcium concentrations, absorption capabilities, and other actions.
- Vitamin D is available either as D2 (ergocalciferol) or D3 (cholecalciferol). Both work equally well for bone health.

Both calcium and vitamin D supplements can increase the risks for kidney stones. If you have a history of kidney stones, discuss with your doctor whether these supplements are appropriate for you.

Calcium supplements can also have other side effects and drug interactions:

- Some people may experience gas, bloating, or constipation. These effects can usually be relieved by increasing fluid and fiber consumption.
- Calcium supplements can interfere with the actions of certain medications such as tetracycline antibiotics, thyroid hormone, and proton pump inhibitors. Iron supplements should not be taken at the same time as calcium supplements.

Exercise

Exercise is very important for slowing the progression of osteoporosis. Although mild exercise does not protect bones, moderate exercise (more than 3 days a week for more than a total of 90 minutes a week) reduces the risk for osteoporosis and fracture in both older men and women. Exercise should be regular and life-long. Before beginning any strenuous exercise program, older patients or those who have serious medical conditions should talk to their doctors.

Specific exercises may be better than others:

- Weight-bearing exercise applies tension to muscle and bone and, in young people, can increase bone density by as much as 2 - 8% a year. In premenopausal women these exercises are very protective. Careful weight training is also very beneficial for middle-aged and older people, especially women.
- Regular brisk long walks improve bone density and mobility. Most older individuals should avoid high-impact aerobic exercises (step aerobics), which increase the risk for osteoporotic fractures. Although low-impact aerobic exercises such as swimming and bicycling do not increase bone density, they are excellent for cardiovascular fitness and should be part of a regular regimen.
- Exercises specifically targeted to strengthen the back may help prevent fractures later on in life and can be beneficial in improving posture and reducing kyphosis (hunchback), even in people with existing severe conditions.
- Low-impact exercises that improve concentration, balance, and strength, particularly yoga and tai chi, may help to decrease the risk of falling.

Exercise plays an important role in the retention of bone density in the aging person. Studies show that exercises requiring muscles to pull on bones cause the bones to retain and possibly gain density.

Other Lifestyle Factors

Other lifestyle changes that can help prevent osteoporosis include:

- Limit alcohol consumption. Excessive drinking is associated with brittle bones.
- Limit caffeine consumption. Caffeine may interfere with the body's ability to absorb calcium.
- Quit smoking. The risk for osteoporosis from cigarette smoking appears to diminish after quitting.

Preventing Falls and Fractures

An important component in reducing the risk for fractures is preventing falls. Risk factors for falling include:

- Slow walking
- Inability to walk in a straight line
- Certain medications (such as tranquilizers and sleeping pills)
- Low blood pressure when rising in the morning
- Poor vision

Recommendations for preventing falls or fractures from falls in elderly people include:

- Exercise to maintain strength and balance if there are no conflicting medical conditions.
- Do not use loose rugs on the floors.
- Move any obstructions to walking, such as loose cords or very low pieces of furniture, away from traveled areas.
- Rooms should be well lit.
- Have regular eye checkups.
- Consider installing grab bars in bathrooms especially near shower, tub, or toilet.

Medications

Two types of drugs are used to prevent and treat osteoporosis:

- *Antiresorptive Drugs*. Antiresorptives include bisphosphonates, hormone replacement therapy, selective estrogen-receptor modulators (SERMs), and calcitonin. Bisphosphonates are the standard drugs used for osteoporosis. These drugs block resorption (preventing bone break down), which slows the rate of bone remodeling, but they cannot rebuild bone. Because resorption and reformation occur naturally as a continuous process, blocking resorption may eventually also reduce bone formation.
- *Anabolic (Bone-Forming) Drugs*. Drugs that rebuild bone are known as anabolics. The primary anabolic drug is low-dose parathyroid hormone (PTH), which is administered through injections. This drug may help restore bone and prevent fractures. PTH is still relatively new, and long-term effects are still unknown. Fluoride is another bone-building drug, but it has limitations and is not commonly used.

Both types of drugs are effective in preventing bone loss and fractures, although they may cause different types of side effects.

Bisphosphonates

Bisphosphonates are the primary drugs for preventing and treating osteoporosis. They can help reduce the risk of both spinal and hip fractures, including among patients with prior bone breaks.

Studies indicate that these drugs are effective and safe for at least 10 years. Eventually, however, bone loss continues with bisphosphonates. This may be due to the fact that bone breakdown is one of two phases in a continuous process of rebuilding bone. Over time, blocking resorption interrupts this process and impairs the second half of the process -- bone formation. Some, but not all, patients who are at low risk for fracture may be able to stop using the drug after 5 years. Other patients need to continue taking this type of drug on a continuous basis.

Candidates. National Osteoporosis Foundation guidelines recommend that the following people should take or consider bisphosphonates:

- Women with a below-normal bone density of 2.5 standard deviation or greater and no history of fractures
- Women with below-normal bone density 1 standard deviation or more and a history of fractures

Brands. Bisphosphonates are available in different forms:

- Oral bisphosphonates. These pills include alendronate (Fosamax, generic), risedronate (Actonel), and ibandronate (Boniva). Alendronate and risedronate are taken once a week. In 2005, ibandronate was approved as the first once-monthly pill. Risedronate is also available in a pill that contains calcium, and is available as a once-a-month pill. Alendronate is also available in a formulation that has vitamin D . Risedronate and alendronate are approved for both men and women.
- Injectable bisphosphonates. In 2007, zoledronic acid (Reclast) was approved as the first once-yearly injection treatment for postmenopausal osteoporosis, and in 2008 was approved to prevent new fractures in patients who have had a hip fracture. The injectable form of ibandronate (Boniva), approved in 2006, requires injections 4 times a year. Injectable bisphosphonates are an alternative for patients who may have difficulty swallowing pills or sitting upright after oral bisphosphonate treatment.

Side Effects. The most distressing side effects of bisphosphonates are gastrointestinal problems, particularly stomach cramps and heartburn. These symptoms are very common and occur in nearly half of all patients. Other side effects may include irritation of the esophagus (the tube that connects the mouth to the stomach) and ulcers in the esophagus or stomach. Some patients may have muscle and joint pain. To avoid stomach problems, doctors recommend:

- Take the pill on an empty stomach in the morning with 6 - 8 ounces of water (not juice or carbonated or mineral water).

- After taking the pill, remain in an upright position. Do not eat or drink for at least 30 - 60 minutes. (Check your drug's dosing instructions for exact time.)
- If you develop chest pain, heartburn, or difficulty swallowing, stop taking the drug and see your doctor.

Other Concerns. Osteonecrosis (bone death) of the jaw is a rare side effect that has occurred mainly in patients who received intravenous bisphosphonates for cancer treatment (not osteoporosis). Many of these patients had major dental procedures before developing osteonecrosis. However, this bone decay condition has also been reported in some patients who have taken bisphosphonates by mouth (mainly alendronate). Symptoms may include jaw pain or swelling, gum infections, and poor healing of the gums. Talk to your doctor or dentist if you experience any jaw or gum discomfort while taking a bisphosphonate drug.

There have also been concerns raised that bisphosphonates may increase the risk for atrial fibrillation, a heart rhythm disorder common in elderly patients. The FDA is monitoring reports of atrial fibrillation among patients who use bisphophonates but at this time does not recommend any changes to prescribing practices. As of late 2008, the FDA had evaluated almost 20,000 patients who had received bisphosphonates without identifying a clear link between these drugs and the risk of atrial fibrillation.

SERMs

Raloxifene (Evista) belongs to a class of drugs called selective estrogen-receptor modulators (SERMs). These drugs are similar, but not identical, to estrogen. Raloxifene provides the bone benefits of estrogen without increasing the risks for estrogen-related breast and uterine cancers. Raloxifene was approved in 1997 to prevent osteoporosis in postmenopausal women, and in 1999 for the treatment of osteoporosis in postmenopausal women. In 2007, the Food and Drug Administration approved raloxifene for prevention of breast cancer in postmenopausal women with osteoporosis, as well as postmenopausal women at high risk for invasive breast cancer.

While there are many SERM drugs, raloxifene is the only one approved for both treatment and prevention of osteoporosis. Only postmenopausal women who have or are at risk for osteoporosis should take this drug. Studies indicate that raloxifene can stop the thinning of bone and help build better quality and stronger bone.

A thrombus is a blood clot that forms in a vessel and remains there. An embolism is a clot that travels from the site where it formed to another location in the body. Thrombi or emboli can lodge in a blood vessel and block the flow of blood in that location, depriving tissues of normal blood flow and oxygen. This can result in damage, destruction (infarction), or even death of the tissues (necrosis) in that area.

Side Effects. Raloxifene increases the risk for blood clots in the veins. Because of this side effect, raloxifene also increases the risk for stroke (but not other types of heart disease). These side effects, though rare, are very serious. Women should not take this drug if they have a history of blood clots, or if they have certain risk factors for stroke and heart disease. More common mild side effects include hot flashes and leg cramps.

Calcitonin

Produced by the thyroid gland, natural calcitonin regulates calcium levels by inhibiting the osteoclastic activity, the breakdown of bone. The drug version is derived from salmon and is available as a nasal spray (Miacalcin) and an injected form (Calcimar). Calcitonin is not used to prevent osteoporosis. It treats osteoporosis. It may be effective for spinal protection (but not hip) in both men and women. Calcitonin may be an alternative for patients who cannot take a bisphosphonate or SERM. It also appears to help relieve bone pain associated with established osteoporosis and fracture.

Side Effects. Side effects include headache, dizziness, anorexia, diarrhea, skin rashes, and edema (swelling). The most common adverse effect experienced with the injection is nausea, with or without vomiting. This occurs less often with the nasal spray. The nasal spray may cause nosebleeds, sinusitis, and inflammation of the membranes in the nose. Also, many people who take calcitonin develop resistance or allergic reactions after long-term use.

Parathyroid Hormone

Teriparatide (Forteo), an injectable drug made from selected amino acids found in parathyroid hormone, can help reduce the risks for spinal and non-spinal fractures. Although high persistent levels of parathyroid hormone (PTH) can cause osteoporosis, daily injections of low and intermittent doses of this hormone actually stimulate bone production and increase bone mineral density.

Side effects of PTH are generally mild and include nausea, dizziness, and leg cramps. No significant complications have been reported to date. A nasal spray version of PTH is currently in clinical trials.

Early animal studies did report bone tumors in mice that were given parathyroid long-term. Such effects have not been observed in humans to date. However, people with Paget disease, (a disorder in which bone thickens but also, oddly, weakens), should not take parathyroid hormone, since they are at higher than normal risk for bone tumors.

Hormone Replacement Therapy

Hormone replacement therapy (HRT) was formerly used to prevent osteoporosis, but is rarely used for this purpose today. Studies have shown that estrogen increases the risk for breast cancer, blood clots, strokes, and heart attacks. For this reason, women need to balance the benefits that HRT has on bone-loss protection, with the risks it carries for other serious health conditions. The FDA recommends that women first try other medications for prevention of osteoporosis.

[For more information on HRT, see *In-Depth Report* #40: Menopause.]

Investigational Drugs

- *New SERMs*. Bazedoxifene (Viviant) and lasofoxifene (Fablyn) are two new selective estrogen receptor modulators (SERMs) that are currently being considered for approval by the FDA. The FDA is weighing the potential benefits of these drugs against their risks, which include stroke. If approved, the FDA may limit these drugs to certain groups of women, such as those at significantly high risk for fractures.
- *Biologic Drugs*. Denosumab is a humanized monoclonal antibody injectable drug currently in phase III studies. It targets the RANK ligand, a protein involved with cells that break down bone (osteoclasts). Odanacatib is another biologic drug currently being investigated. Odanacatib inhibits cathepsin K, a protein that also plays a role in osteoclast activity.

Resources

- www.nof.org -- National Osteoporosis Foundation
- www.niams.nih.gov/Health_Info/Bone -- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- www.iofbonehealth.org -- International Osteoporosis Foundation
- www.healthywomen.org -- National Women's Health Resource Center
- www.menopause.org -- North American Menopause Society