

BUILDING A BETTER MOUSETRAP: TOWARD AN UNDERSTANDING OF OSTEOPOROSIS

There exists a human disease that takes its toll on bones silently and stealthily, weakening them until they break under stresses that should not cause fractures. Osteoporosis is the most common human bone disease. It affects an enormous number of people, and its incidence will only increase as the population ages. This disease is a major public health threat for more than 28 million people in the United States, though 18 million of them do not even know it yet.

Though osteoporosis is associated with aging, osteoporosis is really a childhood disease; it simply doesn't show itself until decades later. Women's bodies stop building new bone by late adolescence; from then on, only maintenance of existing bone is possible. While there is no cure, preventive measures early in life can prevent osteoporosis, or dramatically reduce its impact.

The Foundation for Osteoporosis Research and Education¹ estimates that 90 percent of women older than 75 years of age have osteoporosis. That is

nine of every 10 women in this age group. A woman's lifetime risk of hip fracture is equal to her combined risks of breast, ovarian and uterine cancers, and her lifetime risk of death due to hip fracture is comparable to her risk of death due to breast cancer. Women are at high risk after menopause because they stop producing estrogen, which retards bone loss. Also at risk are overly thin young women who do not produce enough estrogen to menstruate. Women with eating disorders also probably do not get enough calcium, which contributes to their risk. Because near-peak bone mass is usually reached in young women by the age of 20 years, adolescents with eating disorders—who thus already have relatively low bone mass—are particularly in danger.

Men also are at risk: more than 5 million men in the United States either have osteoporosis or low bone-mineral density, which puts them at significant risk of developing the disease.

Detection of osteoporosis is

most easily accomplished through a bone density test. Dual-energy X-ray absorptiometry is one of the most common of these, but dual-photon absorptiometry, ultrasonography and magnetic resonance imaging are other imaging techniques being used or under study. A bone density test can detect osteoporosis before a fracture occurs and can help predict the risk of future fracture. Tests conducted at intervals can determine the rate of bone loss and monitor the effects of osteoporosis treatment. Research is under way to develop blood and urine tests to screen for the disease.

There is no cure for osteoporosis, but there are four therapeutic treatments: estrogens, calcitonin, alendronate and raloxifene²⁻⁴ (Box, "Osteoporosis Treatments").

EFFECTS OF OSTEOPOROSIS

This disease carries a heavy economic burden. Data from 1995 show that osteoporotic hip fractures were the presumed cause

OSTEOPOROSIS TREATMENTS.²⁻⁴

ESTROGEN THERAPIES

Estrogen therapies, also used in the prevention of osteoporosis, can slow bone loss, increase density in both the spine and hip, and reduce the risk of hip and spinal fractures. They also relieve menopausal symptoms and have beneficial effects on cardiovascular health. However, some research has shown an increased risk of breast cancer with use of these therapies; other research has shown no increased risk.

CALCITONIN

Calcitonin is a naturally occurring hormone derived from salmon that can control bone breakdown. In 1995, the Food and Drug Administration approved a nasal-spray version of calcitonin. Daily use of the spray can increase bone mass of the spine but not of the hip.

ALENDRONATE

Alendronate, a biphosphonate, slows bone loss and helps rebuild bone mass by blocking the action of osteoclast cells, which break down bone.

RALOXIFENE

Raloxifene is a selective estrogen receptor modulator, or SERM, that preserves bones and also reduces cholesterol levels. A recent study found that raloxifene helped build bone density in the spine and hip, reduced the risk of spinal fracture and reduced the risk of breast cancer in postmenopausal women.¹ The women were also given supplemental calcium and a form of vitamin D₁.

TREATMENTS UNDER INVESTIGATION

Other treatments under investigation include sodium fluoride, vitamin D metabolites, parathyroid hormone, and other bisphosphonates and SERMs.

of 432,000 hospital admissions, almost 2.5 million physician visits and about 180,000 nursing home admissions in the United States.⁶ Direct health expenditures alone (not including indirect expenses, such as loss of income) were estimated at \$38 million a day.⁶ By one estimate, the number of hip fractures and their associated costs could more than triple by the year 2040.⁶

Osteoporosis also affects the

teeth, the mandible, the maxilla and the craniofacial complex.

Loss of bone mass can lead to loose or lost teeth and resorption of oral alveolar bone. Low bone density can cause dental complications that include the increased risks of periodontal disease and loss of teeth.

Women with severe osteoporosis are three times more likely to experience tooth loss than are women who do not

have osteoporosis; bone loss may be more severe in the mandible than in the maxilla.⁷ Osteoporosis also may be a variable in the etiology, pathogenesis, diagnosis and treatment of temporomandibular disorders and in the outcome of oral and maxillofacial surgery.

A family history of osteoporosis is considered a risk factor for the disease. Peak bone mass levels are somewhat driven by DNA: it is estimated that multiple genetic factors may account for up to 80 percent of a person's peak bone mass potential, while environmental factors account for the rest. Monozygotic twins and parent-offspring models have shown a strong inheritance of peak bone mass, and a familial resemblance in various bone mass measures is detectable well before the pubertal growth spurt.⁸

THE GENETICS OF OSTEOPOROSIS

Studies on the genetics of osteoporosis have rapidly progressed over the past few years. Vitamin D receptor, estrogen receptor and collagen-1-alpha-1 genes all have been studied, and research on many other genes continues. The human genome contains approximately 100,000 genes, each of which may have 10 polymorphisms or variations.⁹

A recent study of apolipoprotein E-4, or APOE-4, found that women with at least one APOE-4 allele had nearly twice the risk of hip fracture and a 67 percent increase in the risk of wrist fracture, compared with women without an APOE-4 allele. However, the effect of APOE-4 on hip fracture was greatest among women with

three or more other risk factors, many of which are environmental (smoking, low calcium intake, excessive alcohol intake, lack of weight-bearing exercise).¹⁰

Researchers at the National Institute of Dental and Craniofacial Research, or NIDCR—along with colleagues at several universities in the United States and Italy—reported last year that mice lacking the gene *biglycan* had low bone mass.¹¹ These “knockout” mice may serve as a useful animal model—or “mousetrap”—for learning about osteoporosis.

Other research has identified a gene, *CBFA1*, at the same location as the gene that causes cleidocranial dysplasia, or CCD, in humans and in mice. CCD is a developmental disorder that stunts the growth of certain bones. The skull of an adult with CCD contains many small bone fragments held together by connective tissue, instead of a few large plates that have fused. Clavicles develop as tiny stumps or not at all. Mice with one mutation at the *CBFA1* locus had symptoms mirroring human CCD, and mice lacking both copies had skeletons made entirely of cartilage.¹² An NIDCR-funded team cloned part of this gene, and found that it is ultimately responsible for the formation of osteoblasts, the bone-building cells in the body.^{13,14}

RESEARCH

Several other components of the National Institutes of Health, or NIH, are currently supporting basic and/or clinical research on osteoporosis and related bone diseases. The National Institute of Arthritis and Musculoskeletal and Skin

Diseases, or NIAMS, initiated the Federal Working Group on Bone Diseases, which provides a forum for the sharing of information between NIH institutes and other federal agencies.

The Basic Osteoporosis New Experimental Strategies initiative—created by NIAMS; the National Institute on Aging, or NIA; and the National Institute of Diabetes and Digestive and Kidney Diseases—is a collaborative effort that encourages established investigators to address osteoporosis-related problems, as well as to increase the pool of investigators

Bone-mineral density predicts hip and other types of fractures, and women with low bone density have an increased risk of stroke.

working in osteoporosis-related basic science areas.

The Study of Osteoporotic Fractures, supported by NIAMS and NIA, involves more than 9,000 women 65 years of age and older. The study demonstrated that bone-mineral density predicts hip and other types of fractures and also provided evidence that women with low bone density have an increased risk of stroke.¹⁵ The NIH Women’s Health Initiative currently supports the largest study of osteoporosis and fractures ever conducted, the goal of which is to determine the usefulness of calcium and vitamin D supplements.

Research ranges from the

painstaking molecular studies described above to “Camp Calcium,” a unique study of calcium balance in adolescents.¹⁶ During summers since 1990, adolescent girls are housed in sorority housing at Purdue University in Indiana. Measures of calcium input and output are completed, but so are typical camp activities, such as field trips, arts and crafts, and sports. The research aims to find out how much calcium adolescent girls need in their diets to maintain the strongest possible bones, and thus reduce their chances of developing osteoporosis later in life. Recently, Camp Calcium began studying adolescent boys as well.

RISK FACTORS

Camp Calcium illustrates an important point: to understand the toll that osteoporosis takes on the aged population, we have to look at the younger population. By about 22 years of age, the average woman has acquired 99 percent of her bone density.¹⁷ In the first five to seven years after she reaches menopause, she can lose up to 20 percent of it. That still is not enough to be detected—conventional radiographs cannot detect osteoporosis until a woman loses 30 percent or even 40 percent of her bone mass. Women who have experienced menopause are at higher risk of losing bone mass, because their bodies produce less estrogen, which helps keep calcium in the bones and maintains bone mass. Men tend to have more bone mass than women and do not have these changes in hormonal milieu. This is why being female is one of the greatest risk factors for osteoporosis.

FOR FURTHER INFORMATION

ORGANIZATIONS**Foundation for Osteoporosis Research and Education**

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The National Institute of Arthritis and Musculoskeletal and Skin Diseases

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The National Institute of Dental and Craniofacial Research

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1-301-496-4261
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The National Institutes of Health

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The National Osteoporosis Foundation

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National Resource Center on Osteoporosis and Related Bone Diseases

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PUBLICATIONS

National Institute of Arthritis and Musculoskeletal and Skin Diseases. Summary—NIAMS workshop, “Genetics of Bone Mass,” June 9-10, 1998, National Institutes of Health, Bethesda, Md. Available at: “<http://www.nih.gov/niams/reports/genesum.htm>”. Accessed Sept. 27, 1999.

Inadequate calcium intake is another major risk factor. An average adult body contains about 1,000 grams (2.2 pounds) of calcium, 99 percent of it in the bones and teeth. We lose calcium daily, mostly through sweat, urine and feces. Optimal calcium intakes range from 44 milligrams per day for infants to 1,500 mg per day for adolescents, young adults, pregnant or lactating women, postmenopausal women who are not receiving estrogen replacement therapy and everyone older than the age of 65 years.

Camp Calcium research has shown that calcium absorption differs markedly by age; girls absorb 38 percent of their calcium intake, while young women absorb 22 percent.¹⁸ Girls excreted less calcium in their urine and deposited more in bone than did young women.¹⁸ The peak age for calcium retention is before the onset of menstruation; by age 21 years, women lose as much calcium as they take in.¹⁹ Complicating the problem is a tendency for adolescent girls to be concerned about weight gain and to decrease intake of dairy products accordingly. At the age when they could be building bones, many girls are consuming less than one-half the recommended amount of calcium. A 1997 study found that the smallest intake of calcium that allowed some girls to absorb maximal calcium was 1,300 mg, which falls within the 1,200- to 1,500-mg range recommended for females aged 11 to 24 years.²⁰

A lack of weight-bearing exercise is another risk factor for osteoporosis. Such exercise—running/jogging, walking, hiking, racquet sports, danc-

ing—helps build bone mass. Only 20 percent of Americans exercise regularly; this means that most of us are sedentary, which increases the risk of developing not only osteoporosis but also a myriad of other diseases and conditions. A landmark study conducted by Tufts University examined 40 postmenopausal women 50 to 70 years of age—all healthy, but sedentary. None was taking artificial estrogen. One-half maintained their usual routines, while the other one-half lifted weights at 70 to 80 percent of their capacity twice a week. One year later, the women who did not exercise were less active than before. They had lost muscle and bone density and gained body fat. The exercisers, however, traded fat for muscle, improved their balance and gained strength and small, but significant, amounts of bone density.²¹ Those who take certain medications—such as steroids, anticonvulsants, certain cancer-treatment drugs or aluminum-containing antacids—may further increase their risk of osteoporosis, as may people with chronic diseases that alter hormone levels.

CONCLUSION

Considering the tremendous social and economic burden of osteoporosis, discourse about it is rare. We worry about cancer, about heart attacks and strokes, but osteoporosis stays in the background. The “silent disease” remains silent. A 1991 Gallup poll, commissioned by the National Osteoporosis Foundation, found that three-fourths of women 45 to 75 years of age—the group at highest risk of developing the disease—had never discussed osteo-



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porosis with their health care providers.

Yet this disease causes 1.5 million fractures annually, 300,000 of them hip fractures. Women have two to three times as many hip fractures as men,

but men have twice the mortality rate that women do in the year after a hip fracture. About one-half of the people with hip fractures end up in nursing homes, and in the year following the fracture, 20 percent of them die. Another 25 percent may require long-term nursing home care, and only one-third fully regain a prefracture level of independence. Hip and vertebral fractures also can cause psychological symptoms—most notably, depression—as patients deal with pain, physical limitation and lifestyle changes. The high morbidity and consequent dependence associated with osteoporotic fractures are a strain on patients and their families.

Osteoporosis is an epidemic.

It's easy to ignore a disease that takes so long to show itself, and that has so few symptoms. Health promotion and disease prevention are difficult; the human mind prefers observed change to maintained equilibrium. Even so, scientists around the world are on their way to understanding how osteoporosis occurs and finding better ways to promote health and to prevent, diagnose and treat disease. ■

The views expressed are those of the author and do not necessarily reflect the opinions or official policies of the American Dental Association.

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