OSTEOPOROSIS IN BIOCULTURAL PERSPECTIVE

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KEY WORDS: bone, fractures, menopause, calcium homeostasis, skeleton

ABSTRACT

Osteoporosis is a condition in which loss of bone density leads to increased risk of fracture. This condition is increasing in frequency in most parts of the world and has become a major cause of medical expenditures in the United States, where it is estimated to cost nearly $10 billion per year. European countries report similar increases in the proportion of their medical costs attributable to osteoporosis. In most cases, osteoporosis, which occurs earlier and more frequently in women, is associated with age-related endocrine changes, especially the decline in estrogen production occurring at menopause. However, earlier occurrence resulting from factors such as inactivity, low bone peak density in early adulthood, low calcium intake, and a variety of dietary and lifestyle factors can lead to high risk of fracture before menopause. This is because bone is in a continual state of turnover, and the balance between bone formation and resorption can be upset by a number of endogenous and exogenous factors. Relatively inefficient intestinal absorption of calcium, which can increase the risk of osteoporosis, is probably an adaptation that avoids the necessity of excessive kidney excretion of calcium. Modern lifestyles and increased life expectancies are exposing the biological cost of this adaptation.

WHAT IS OSTEOPOROSIS?

In this review, osteoporosis is defined as low bone density associated with increased risk of fractures not caused by serious trauma. Although
osteoarthritis is usually thought of in terms of its clinical significance, it is also of interest because of its increased incidence in recent years and because it may be one of a number of degenerative changes that limit human life span. As such, the current increase in the incidence of osteoporosis might be evidence of evolutionary forces that acted on earlier human populations living much shorter lives under more rigorous selective pressure.

Clinical Diagnosis

Bone Densitometry Osteoporosis is diagnosed by measuring the density of bone at one or a number of sites. Techniques commonly used include radiographic (X-ray) images, single- and dual-photon absorptiometry (SPA and DPA) (129, 235), and dual-energy X-ray analysis (DEXA). Other, more elaborate and more invasive methods such as quantitative computed tomography (qCT) (49) and computer-assisted tomography (CAT) also have been used. Normative values for bone densities at various sites have been determined by laboratory analysis of representative samples of bone in vitro and in large populations of human subjects of all ages in vivo. To assess the relative fracture risk of a subject, these normative values are compared to bone density values obtained at sites of clinical significance, usually in the spine, the hip, and the forearm. Forearm scans can be taken economically using SPA, while measurement of the spine and hip require DPA or DEXA instrumentation. Whole-body determinations can be made using DEXA, and estimations of soft-tissue compartments are also possible, making this method valuable for both clinical and research purposes.

Table 1 shows the bone density values for 5-year age categories for individuals of both sexes drawn from a 12-year longitudinal study conducted in Arizona (209). Values characteristic of a young normal individual (30–35 years of age) of each sex form the basis for comparison. The ratio of the subject’s bone density to that of the “young normal” is calculated to estimate the risk of fracture attributable to loss of bone density. Values exceeding 90% of young normal are considered normal, whereas those falling between 80% and 90% indicate mild risk, those below 80% indicate moderate risk, and those below 70% indicate extreme risk. Heightened risk of fracture is suggested when bone density values fall two standard deviations below young normal.

Applying these criteria, Melton et al (138, 139) found 45% of a Minnesota sample of Caucasian women over 50 years of age at risk at one or more sites. Of these subjects, 32% had low values in the spine, 29% in the hip, and 26% in the forearm. These observed risk values indicate a lifetime fracture probability of 40% (10). Other investigators, including Chrischilles et al (39), calculate the risk at 54%. They estimate that osteoporosis-related fractures will cause 6.7% of American women to become dependent on the help of others to conduct the
Table 1  Bone densities of Arizona women compared with those of women from five Chinese locations. Values are averages for 5-year age groups. Density values obtained by single photon absorptiometry (SPA) (209).

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| 55-64 | 0.77 | 0.59 | 0.73 | 0.61 | 0.69 | 0.58 |
| 65-75 | 0.68 | 0.52 | 0.65 | 0.54 | 0.61 | 0.52 |

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BMD (g/cm) and BMD (g/cm**2) both taken at the distal 1/3 site

basic activities of daily living, while an additional 7.8% will require nursing home care for an average of 7.6 years. It has been estimated that hip fractures alone are responsible for medical expenses in excess of $10 billion annually in the United States. With female life expectancy at birth in the United States now exceeding 80 years, hip fractures will be of increasing concern for future generations. Once bone loss begins, it usually continues and may even accelerate after the age of 70 (99).

Vertebral crush fractures will also become more common as the aging population increases. The incidence of such fractures is currently 17.1/10,000 white women per year compared to 9.9/10,000 for white men. For African-American women the incidence is 3.7/10,000, and for African-American men it is 2.5/10,000 (94).

BIOCHEMICAL MARKERS OF BONE TURNOVER  Evidence of bone mineral turnover can also be obtained from blood, urine, and fecal samples. Bone formation is reflected in increased serum concentrations of alkaline phosphatase, osteocalcin, and Type I collagen extension peptides. Bone resorption can be detected by a rise in the plasma concentration of tartrate-resistant acid phosphatase and by measurement of fasting urinary calcium and hydroxyproline, urinary hydroxylysine glycosides, and urinary excretion of pyridinium cross-links pyridinoline.
and deoxypyridinoline (50, 51, 81, 89, 153, 172, 178, 185, 190). Fecal calcium loss, although not a direct measure of bone turnover, can indicate poor intestinal calcium absorption. In some cases, poor calcium absorption may be a major predisposing condition for the onset of osteoporosis. Age-related changes in the gastrointestinal tract, such as reduced acid production in the stomach, can profoundly alter absorption of calcium and other nutrients.

WORLDWIDE DISTRIBUTION OF OSTEOPOROSIS

A number of countries have experienced increased incidence of osteoporosis-related injuries. The incidence of hip fractures in Switzerland (163) has been estimated at 14.7/10,000 for women and 4.0/10,000 for men, with an annual cost of 200 million francs (25). In Italy the incidence has been reported at 16.9/10,000 for women, and the female-to-male ratio for hip fractures is 3.5:1 (136). High incidences have also been reported from Finland (227), France (10), and Poland (144). Taiwan (201), Japan (67a), and Hong Kong (113a) are also experiencing increases in the incidence of osteoporosis-related fractures.

Fracture incidence appears to be higher among Caucasian populations than among Asian or African ones. Also, the high female-to-male ratios of hip fracture incidence seen in populations of European descent have not been reported in African and Asian populations, where hip fracture incidence among males sometimes exceeds that of females (124). Numerous investigators have reported lower fracture susceptibility in African and African-derived populations. Superior bone density values throughout life are an attribute of African heritage (8, 17, 20, 24, 38, 41, 46, 72, 75, 76, 79, 139, 146, 167, 176, 196, 197, 222–224).

Several investigators have reported low bone density values for Asian and Native American populations, including Eskimos (73, 82, 135, 159, 233, 243). However, there is considerable heterogeneity among Asian populations, some Chinese populations have young adult bone density values exceeding those of age- and sex-matched Caucasian-Americans (90, 91, 210). Fujita et al (68, 69) report distinct differences in Japanese seacoast populations compared to mountain dwellers. Therefore, although ethnically defined populations tend to conform to characteristic bone density patterns, exceptions indicate significant environmental influence on the attainment of peak bone density.

TYPES OF OSTEOPOROSIS

Riggs & Melton (187) have proposed terms that distinguish between two distinct forms of osteoporosis. The first, designated Type I, occurs most frequently in women and is associated with the endocrine changes of menopause. The second, Type II osteoporosis, is generally of later onset, occurs both in
women and men, and has sometimes been referred to as "senile osteoporosis." In Type I osteoporosis, loss of the honeycomb-like trabecular bone located in the marrow-containing interior areas of bone predominates. Because of its honeycomb-like structure, the mineral in trabecular bone has a higher proportion of surface to mass than does the harder, denser cortical bone that forms the outer surface of bone. Thus, trabecular bone is more accessible to physiological changes and maintains a higher rate of turnover throughout life. The high proportion of trabecular bone in the spinal column and proximal femur makes these sites susceptible to fracture because much of the bone lost at menopause is of the trabecular category (189). Such fractures are therefore considered indicators of Type I osteoporosis. This is particularly true of vertebral crush fractures (54, 140), although spine fractures are not always predictive of hip fracture susceptibility (109).

Crush fractures may be symmetrical or may result in "wedging." Both wedging and total collapse occur most frequently in the thoracic and lumbar vertebrae, especially the segment from the eighth thoracic (T-8) to the third lumbar (L-3) vertebra. The twelfth thoracic vertebra (T-12) is often the first to collapse (240). The cumulative effect of a number of vertebral crush fractures can result in a pronounced dorsal curvature of the spine commonly called the Dowager's hump. The shortening of the spine associated with this condition produces a reduction in the volume of the pulmonary and abdominal cavities. Severe cases lead to serious respiratory and/or digestive problems that can ultimately become life threatening (77, 88, 106, 200). The frequency of hip fractures and Colle's fracture of the forearm in peri- and post-menopausal women is also associated with the presence of a high proportion of trabecular bone at the sites of fracture. These fractures are also considered indicators of Type I osteoporosis.

The rapid phase of bone loss at menopause does not continue indefinitely. Five to ten years after menopause, female bone density loss slows to a rate similar to that of males. However, since female peak bone mass is substantially less than male, the period of accelerated loss places many more women than men at risk for Type I fractures.

Type I osteoporosis, although largely involving trabecular bone, also may affect cortical bone. Formation of absorption cavities can result in trabeculation of cortical bone prior to its removal (103, 160a). Decline in the repair of microfractures may also make cortical bone more susceptible to resorption and ultimately fracture (64, 66, 67). Slowing rates of bone turnover may also be implicated in cortical bone brittleness and fracture as a result of hypermineralization (169). Although the occurrence of menopause results in higher frequencies of Type I osteoporosis in women, it can occur in aging men as well (60, 137, 158, 165), and castration increases a man's risk for osteoporosis-related fractures substantially (207).
Although Type I osteoporosis is sometimes referred to as postmenopausal osteoporosis, such terminology is problematic because a similar pattern of bone loss occurs in men and trabecular bone loss continues long after the period of accelerated bone loss associated with menopause. However, later loss of bone, sometimes called senile osteoporosis, increasingly involves cortical bone. Progressive thinning of the cortex of the long bones becomes predominant as the amount of trabecular bone available for resorption decreases. The mechanisms producing cortical bone loss appear to be similar in both sexes, although a greater degree of remodeling of cortical cross-sectional area may occur in women (210).

BONE STRUCTURE, FUNCTION, AND HOMEOSTASIS

Bone Structure and Histology

Calcium stored in the human skeleton represents 98% of the body's total pool of calcium (52, 104, 133, 161a, 221). Most of the skeleton's calcium is in the form of calcium hydroxyapatite, a crystalline aggregate that also contains phosphate groups and hydroxy ions. Newly formed hydroxyapatite crystals are different than older ones in that older crystals are larger, more regular, and contain less carbonate (21, 177, 217). The difference in crystalline structure results in older crystals offering less surface area where resorption can occur.

TRABECULAR BONE The spongy, lighter form of bone referred to as trabecular or cancellous bone is most abundant in the axial skeleton where, excluding the skull, it makes up 90% of the total bone present. It is usually found in protected areas such as in the marrow cavities near the ends of long bones, in the bodies of vertebrae, in the ribs, and in the bones of the pelvis. Trabecular bone is made up of a combination of vertical struts and horizontal plates that form an open latticework in which 30–90% of the enclosed area is open space (31). The strength of this latticework depends on the density of structural components and on their connectedness (141, 170, 168, 238). The orientation and the density of trabeculae develop along lines determined by stresses experienced during growth.

As long as the latticework remains intact and the stresses remain similar to those experienced during growth, trabecular bone in the hip or spine is well suited to withstand compressional stress associated with weight-bearing activities. But, because of its greater accessibility for resorption, trabecular bone is usually the first element of the skeleton to experience loss of mass when aging, illness, or other factors precipitate mobilization of calcium.

Although there may be some remodeling of trabecular bone under prolonged stress (111), when it is resorbed, it is usually not replaced. Cortical
bone is continually undergoing remodeling, but trabecular bone gradually diminishes in quantity. According to Heaney (84), loss of horizontal plates leads to the buckling of vertical struts and a cumulative loss of the connectedness upon which the strength of trabecular bone depends. As weight-bearing capacity of the trabeculae declines, their contribution to the overall structural integrity of the bone diminishes, increasing stress on the cortical component, ultimately to the point where it fails and a fracture occurs (42). Therefore, the risk of failure under stress is greatest at sites where trabecular bone plays a major role in weight-bearing activities. In humans, this usually occurs earliest in the vertebral column, which is about 40% trabecular bone (74).

The high incidence of vertebral crush fractures and hip fractures in peri- and postmenopausal women reflects trabecular bone loss. Early in life, trabecular bone is the most metabolically active compartment of bone, making it the most vulnerable to perturbations of the balance of bone turnover (96) and the first to exhibit the symptoms of osteopenia, or abnormally low density of bone (51a, 110a). Trabecular thinning that has progressed to the point where loss of connectedness has also occurred leads to heightened risk of fracture.

CORTICAL BONE  Cortical or compact bone, which is denser than trabecular bone, makes up about 80% of the total mass of bone in the human skeleton (175). It forms the outer surface of bones that may have a high proportion of trabecular bone inside. In humans the appendicular skeleton (that part of the skeleton forming the limbs, as opposed to the axial skeleton, made up of the spine and skull) is 95% compact bone by volume (132). Because of its greater density it is superior to trabecular bone in impact resistance. In the shaft of long bones, cortical bone also functions as a major weight-bearing structure. Located on the surface of long bones, at the sites of tendinous insertions, cortical bone is also subjected to variable amounts of tensional stress as muscles contract to effect movement. In addition, there are many occasions when the shaft of a long bone will be twisted around its long axis, creating torsional stress. The structure of cortical bone is far better suited to cope with this range of stresses than is trabecular bone. The pattern of its distribution throughout the skeleton reflects the nature and magnitude of stresses encountered in each region.

The characteristic structural unit of cortical bone is the osteon, which consists of a blood vessel around which concentric layers or lamellae of bone are deposited (Figure 1). Each layer is connected to the others by a network of small canals (canaliculae) filled with endolymph, a thin, serous fluid that functions as a medium for the diffusion and transport of nutrients and metabolic byproducts into and out of the system. Throughout the system there are a number of openings (lacunae) occupied by living bone cells (osteocytes). The entire system, referred to as a Haversian system, functions as an intercon-
nected network for the exchange of nutrients and metabolic byproducts between even the densest sectors of bone and the vascular system.

With age and remodeling, the original primary osteons are resorbed wholly or in part and are replaced by secondary osteons. Portions of older lamellae remain between osteons (interstitial lamellae), and the system eventually takes on a less organized appearance. As a result of differential rates of remodeling, some bony features may even drift into different positions (56, 65). The remodeling of cortical bone occurs at different rates in different parts of the skeleton. It occurs more rapidly in the femur, for instance, where cortical bone has a half-life of approximately 7.6 years, than in the tibia, where a half-life of 24.2 years is normal. As a result, there is considerable heterogeneity in the organization of cortical bone (84, 85).

The remodeling of cortical bone takes place in three envelopes simultaneously, although by no means at identical rates. Most active in long-bone remodeling is the endosteal envelope, located adjacent to the medullary (marrow) cavity on the interior surface of the bone. Remodeling also occurs in the periosteal envelope on the exterior surface and within the Haversian systems themselves. Cortical bone turnover in the young individual is "coupled," with resorption and deposition occurring in progressive phases (62, 95). According

![Figure 1](image-url)  
*Figure 1* Haversian systems (osteons), the basic structural units of cortical bone.
to Frost (64), the process begins with activation, followed by osteoclastic resorption, and finally, formation of new bone. The team of cells collaborating in this process has been called the basic multicellular unit (BMU) of bone remodeling. The unit includes both the osteoclasts that resorb bone and the osteoblasts that replace it (63, 64). Any disturbance of the sequence by which old bone is replaced by new can lead to excessive cortical bone loss and, ultimately, to osteoporosis.

Osteoclastic resorption of bone usually takes place at sites where the local strains of compression and torsion are greatest. Replacement takes longer than resorption. Even after osteoblasts have deposited a new matrix there is a delay of about eight days before mineralization begins. This is a period of vulnerability to deficiencies in bone replacement. Even under normal circumstances, a truly steady-state of bone density is probably seldom achieved (97). Most often, the pattern in the long bones involves enlargement of the medullary cavity through endosteal resorption, and the amount of bone resorbed is greater than that added (95, 142). Even when there is no net gain or loss of bone mass, there usually is a net gain in osteon number in the periosteal envelope. However, there is also a decline in quality because of the replacement of more stable, primary osteons by new bone. Recent evidence indicates that mineralization decreases with increasing distance from the Haversian canal of remodeled cortical bone (45). As a result of this combination of remodeling events, long bones tend to gain external diameter while experiencing a thinning of the cortex (128, 168, 210).

Up to a point, the expanded diameter of the diaphysis, or shaft, of long bones confers a mechanical advantage. Increased cross-sectional area of a long bone alters its cross-sectional moment of inertia (CSMI), which is closely related to its resistance to bending stress (26, 114, 115, 129, 210). The mass of bone mineral present and its distribution relative to the neutral axis of the bone determine the bone’s resistance to bending stress. Mass distributed farther from the neutral axis makes a greater contribution to stress resistance than does mass closer to the cross-sectional center of the bone. Because of this mechanical relationship in the approximately cylindrical shaft of a long bone, mineral located on the outside of the periosteal surface confers greater stress resistance than does mineral located on the endosteal surface. Thus, adding bone to the periosteal surface can compensate for endosteal resorption even when there is a net loss of bone mineral (26, 34, 191, 192).

Although reduced risk of fracture is an adaptive response to this form of stress exposure, there is a limit to the benefit that can be conferred by such an adaptive strategy. If the cortex of the bone is excessively thinned in response to bending stress, the end result will eventually be increased risk of fracture due to buckling. Such buckling fractures are often associated with torsional
stress that occurs during a fall. The Colle’s fracture of the wrist, common in middle-aged and older women, is a classic example of this type of fracture.

Mechanical stresses are known to cause sufficient fatigue in cortical bone to produce microcracks, which Frost (65) believes stimulate repair mechanisms. The heterogeneity of bone quality from point to point on a specific bone’s surface makes bone relatively more susceptible to fatigue damage than would be the case if the surface was of the same quality at all points (32, 33). Severe compressive stress will produce shear cracks in cortical bone, almost certainy inflicting damage on bone cells in the damaged area. Severe tensile strain causes debonding of osteons, although it is not thought to cause cellular damage. Osteoid or primary bone, lacking Haversian systems, seems to have better resistance to tensile strains than does Haversian bone (232), but osteons limit damage by reducing the spread of cracks that would propagate farther in a homogeneous medium (47). Evidence that fatigue damage stimulates Haversian remodeling is cited by Burr et al (27), who observed substantial increases in resorative activity a few days after the appearance of microcracks in cortical bone.

Up to 90% of the compressive strength of compact bone is determined by its density (133, 134). Loss of bone mass means loss of bone strength, which in turn means increased risk of fracture, the current clinical definition of osteoporosis.

RISK FACTORS

Genetic Predisposition

Small, slender women with light complexions are often at high-risk for osteoporosis. Twin studies suggest a genetic basis for this risk. Some of the factors involved in the attainment of low peak bone density, the major risk factor for osteoporosis (13, 40, 43, 98, 113, 121, 156, 188, 198, 212), have been identified. Tokita et al (218) studied pairs of monozygotic and dizygotic female twins to isolate genetically determined differences in the synthesis and degradation of Type I collagen related to low bone density. Focusing on the coding sequence for Type I procollagen in osteogenesis imperfecta, an inherited condition in which faulty collagen formation results in weak, easily fractured bones, Spotila et al (206) identified several mutations. Cassella et al (35) found abnormalities in the Type I collagen fibrils of osteogenesis imperfecta patients that they believe affect the formation and stability of the bone mineral associated with it. Inherited variations in the vitamin D receptor associated with low bone density and osteoporotic fractures have also been reported (53, 148, 149, 161).
Reproductive History

On average, bone mineral densities of childless women are lower than those of women who have borne children (70, 155). Moreover, there appears to be a continuous upward trend in bone density values as the number of children borne increases even after controlling for confounding factors such as age, body mass index (BMI), menopausal status, oral contraceptive use, smoking habits, and breastfeeding status. Murphy et al (155) report a 1% average increase in bone density at all sites per live birth. The improved calcium absorption efficiency associated with pregnancy and breastfeeding appears to confer long-term benefits.

Lifestyle Factors

EXERCISE Insufficient activity, especially of the weight-bearing category, accelerates loss of bone density. The experience of astronauts and cosmonauts in the microgravity of space travel is an extreme but informative example. Long-term space travelers have lost up to 18% of weight-bearing bone during extended flights (91a). Some form of weight-bearing exercise is essential to maintain bone density, but the optimum amount of exercise differs between the sexes and among individuals (93). High-impact exercise appears to have the greatest positive effect (15). However, excessive exercise, especially in women, can decrease bone density. This decrease has been associated with a reduction in circulating estrogens found in women with high activity levels. The impact is perhaps greatest in young women who have not yet attained peak bone density and who therefore have less bone mineral reserve to draw on at menopause (203, 220, 244). The effect of anorexia nervosa is similar to that of excessive leanness in general (199).

DIETARY FACTORS Adequate calcium intake is essential to maintain physiological homeostasis, although how much calcium is enough is uncertain. Calcium intakes vary widely in different populations. Even within a single country, China reported daily calcium intake may range from a low of 230 mg to a high of 724 mg (90, 91, 210). This wide range may indicate early adaptations to low intakes. Few populations achieve the 1000 mg per day recommended for young women in the United States.

Calcium ingested in dairy products, particularly before age 25, is associated with higher bone densities in women (154). Half a liter of milk and 25 g of cheese per day will satisfy calcium requirements for most people (145). Other foods, including broccoli, cabbage, beans, and some dark green, leafy vegetables, are also good sources of calcium. Fish consumed with bones provides dietary calcium without much fat. Elderly female lactoovovegetarians have been found to maintain bone density as well as omnivores at a calcium intake
25% below the omnivore level (180). However, calcium intake early in life is positively correlated with peak bone density (131, 179).

Much of the controversy over recommended calcium intake is focused on the benefits of calcium supplements later in life. Several studies have shown no positive effect of calcium intake on the rate of bone mineral decline with aging (16, 159, 180, 205). The importance of adequate synthesis or ingestion of vitamin D (160) may necessitate supplementation when sun exposure is inadequate and/or dietary intake is insufficient.

High protein diets increase the level of calcium excretion (23, 164, 226, 244), as a result of the increased acidity of the urine associated with such diets. Increased acid secretion by the kidney is caused by oxidation of the sulfur-containing amino acids methionine and cysteine, abundant in animal proteins (36, 245). A more acidic urine leads to greater excretion of calcium (117, 171, 195), because high acidity requires buffering and calcium is an important buffer (116, 234). Urinary calcium loss stimulates bone resorption (5, 7, 87, 119, 236), resulting in a linear relationship between animal protein intake and urinary calcium loss (102). Thus high lifelong intakes of animal protein in many Western countries may be an important risk factor for osteoporosis (1, 120, 163a, 242). Lower demand for calcium buffering may be instrumental in the superior bone densities maintained by vegetarians (55, 92, 123, 126, 214, 228). Cross-cultural comparisons indicate a strong association between diets high in animal protein and incidence of hip fracture (1, 37, 91). The low calcium-to-phosphorus ratio of animal protein has also been shown to induce mild secondary hyperparathyroidism (28–30).

ALCOHOL CONSUMPTION Even moderate alcohol consumption can increase bone loss in many individuals (112, 157), perhaps because of its effect of reducing osteoblast activity. In males, prolonged excessive alcohol intake is associated with hypogonadism, and acute alcohol intoxication also causes transitory hypoparathyroidism with excessive urinary calcium loss. Chronic alcoholics often have low serum concentrations of vitamin D metabolites as well. They also often express low testosterone levels associated with the aforementioned hypogonadism with a concomitant increase in fracture risk. Testosterone supplementation in hypogonadal males has been shown to have a positive effect on bone density (193, 231a).

CAFFEINE Caffeine may also have a negative effect on bone density (14, 130). Loss of bone mineral may result from increased urinary calcium loss, along with magnesium, sodium, and chloride, for a three-hour period following ingestion of caffeine-containing beverages. This effect is greater in older than in younger women. The loss may be offset partially by milk consumption. Cola drinks, which frequently displace milk in the adolescent diet and which contain phos-
phorus, have a negative effect on bone density as well, and their regular use is associated with increased fracture rates in women. This effect has not been shown to occur in males (241).

**Medications**

Thyroid hormone supplementation has a negative effect on bone density (61, 194), although estrogen use may negate this effect in postmenopausal women. Corticosteroids suppress bone formation, leading to what has been termed steroid osteoporosis (48, 108, 122, 186).

**TREATMENTS**

**Hormone Replacement**

Hormone replacement therapy (HRT) has been the most consistently effective treatment for prevention of osteoporosis in women (78, 83, 122, 127, 208), although HRT may be less effective in preventing Type II osteoporosis than Type I (231a). As mentioned earlier, both testosterone and growth hormone supplementation have slowed bone loss in men. Thiazide diuretic drugs have been found to reduce bone loss in a sample of elderly Japanese-American men living in Hawaii (237) and appear to have enhanced the effect of estrogen in a large sample of Caucasian women in California (150).

**Fluorides**

Sodium fluoride has a positive effect on bone density of the spine (19), but its benefits may be offset by sufficient toxicity to make its use inadvisable (105). Some investigators consider it ineffective (100, 216). There is evidence that although fluoride treatment produces short-term improvements in bone density, over a five-year period the result may be a 40% decrease in bone quality and strength (204). The major problem with the use of fluorides is the difficulty of determining appropriate dosage for long-term treatment.

**Calcitonin**

Calcitonin, produced by the thyroid, has a powerful effect on fast-turnover bone loss. It was formerly administered by injection, but more recently, nasal sprays and rectal suppositories have been found to deliver effective doses. With the advent of these routes of therapy, a number of clinicians have recommended calcitonin for treatment of osteoporosis (9, 58, 59, 107, 125, 151, 162, 174, 181, 183, 184, 207, 209, 211, 215, 219, 225, 230, 239). One of the benefits of calcitonin is its analgesic effect, which may arise from an increase in beta-endorphin release, at least when nonsteroidal anti-inflammatory drugs are also taken (12). It may be possible to combine calcitonin in some form with
other medications to enhance its effectiveness. Although calcitonin’s effectiveness is reduced by simultaneous treatment with calcitriol (57), a combination of calcitonin and etidronate was found highly effective in reducing the hypercalcemia of immobilization (143). Szucs et al (213) found that a combination of calcitonin and the anabolic steroid norandrostenumone decanoate reduced bone density loss.

Calcitonin reduces serum testosterone, luteinizing hormone, and follicle-stimulating hormone. This observation suggests that calcitonin and testosterone interact in a negative-feedback system (152). A potential problem with the long-term use of calcitonin from other species, such as salmon, is that eventually the patient produces antibodies against it (183, 184), although these antibodies do not seem to alter calcitonin’s effectiveness. Some investigators, however, have found calcitonin treatment to be ineffective (2, 57).

**Bisphosphanates**

One member of the bisphosphonate group, clodranate, was found in one trial to be more effective than calcitonin (173), possibly less potent than another bisphosphonate, pamidronate, but of equal potency to two others, etidronate and alendronate. Several other investigators report success with clodranate (101, 118, 202). Adami et al (2) report increases in bone densities in both the spine and hip of patients treated with alendronate, and Hall & Schaiff (80) report similar success using pamidronate. However, there are questions concerning the quality of bone added during this kind of treatment and its long-term stability. There is also concern about a possible toxic effect on osteoclasts by some of the bisphosphonates. Etidronate blocks mineralization as well as resorption and thus has the potential to induce loss of bone mineral (166).

**Ipriflavones and Experimental Drugs**

A number of investigators have reported successful treatment of osteoporosis using ipriflavone (3, 4, 11, 18, 44, 71, 110, 147, 182, 229). This medication is thought to inhibit prostaglandin release and the formation and activity of osteoclasts through modulation of intracellular free calcium. Ipriflavone’s major effect is on bone resorption, although Valente et al (229) believe that it may enhance osteoblast function as well. Other new compounds under study for the treatment of osteoporosis include imidazoquinazolinones, methylxanthines, and benzothiophenes (6).

**EVOLUTIONARY SIGNIFICANCE OF INCREASING INCIDENCE OF OSTEOPOROSIS**

As important as it is to maintain an adequate concentration of calcium in the blood, an excessive calcium concentration can lead to harmful and potentially
lethal consequences. At a concentration of 13 mg% calcification of soft tissue will occur. Even more serious is the formation of urolithiases and the resultant damage to the kidneys that sustained hypercalcemia inflicts. Consequently, calcium homeostasis includes mechanisms to protect against increases as well as decreases in serum calcium concentration.

Calcium is unquestionably one of the minerals most essential to life. Perhaps this is because of its abundance: it is the fifth most abundant element in the earth’s crust. The natural diets of mammals are rich in calcium. According to Heaney (86), the diet of early Homo sapiens contained 2000 to 3000 mg of calcium per day. This is three to five times the median calcium intake of US adults today. If we accept the premise that the physiology of human calcium homeostasis evolved in an environment characterized by an abundance of calcium, inefficient intestinal absorption and renal conservation of calcium does not seem paradoxical. In fact, a system more effective in the avoidance of excessive serum calcium concentrations than in the support of high concentrations makes good sense. The normal human serum calcium concentration of 10 mg% is lower than that found in many other organisms, especially marine organisms, which maintain a fluid calcium concentration very close to that of sea water, roughly four times as high as in humans. The maintenance of such a low calcium concentration is itself an adaptation.

An important mechanism for the avoidance of hypercalcemia is tolerance for lessening of calcium absorption efficiency in the intestine when calcium is abundant. Human calcium absorption functions at low efficiency under most circumstances. However, there are times in the human life cycle when absorption efficiency improves dramatically. Hormonal changes occurring during the adolescent growth spurt, pregnancy, and breast-feeding increase absorption efficiency appreciably (Figure 2).

Under normal circumstances, urinary loss of calcium is less than the 60 mg lost in sweat at normal work loads. When the 100 mg of calcium lost in sweat and urine is compared to the 900 mg daily fecal loss when calcium intake is 1000 mg per day, it can be seen that any major improvements in calcium retention must come from alterations in intestinal absorption and secretion. Because osteoporosis ultimately derives from loss of calcium from bone due to insufficient intake, excessive excretion, or both, understanding the role of the intestine in the etiology of osteoporosis is clearly essential.

Widespread increases in the incidence of osteoporosis expose the order of priorities governing human calcium homeostasis. First and foremost is the stringent requirement that calcium be available for its most ancient and basic functions: regulation of muscle contraction, nerve impulse conduction, modulation of cell membrane permeability, and inter- and intra-cellular communication. Its role as a component of bone mineral came later and, although of great importance, is of lower priority. Like many other mammals, humans are en-
Figure 2 The human calcium absorption curve at different intake levels and physiological states. The upper curve shows the increased efficiency of absorption experienced during pregnancy, puberty, and lactation. The middle curve shows the net calcium absorbed at increasing levels of intake in normal adults and during menopause. The bottom curve shows the level of absorption experienced by individuals whose lifetime intakes are high. Note that during pregnancy, a woman may absorb 350 mg of calcium from an intake of 800 mg while an adult whose lifetime intake averages 1100 mg/day may absorb as little as 100 mg. This illustrates the “saturable” characteristic of the human calcium absorption, in which increasingly higher intakes yield a decreasing proportion of absorption (160).

dowed with a relatively inefficient system for absorbing calcium in the intestine. For the most part, this inefficiency facilitates avoidance of life-threatening kidney damage associated with sustained high levels of calcium excretion.

However, a system that worked well in the past seems to have some serious defects for contemporary populations. The increasing incidence of osteoporosis reflects the increasing life expectancies enjoyed by most of the world’s population. Osteoporosis, which usually occurs after menopause in women and later in men, is usually associated with the post-reproductive phase of the human life cycle. As such, the intensity of natural selection against its genetic determinants is weak. Such traits are free to accumulate in a population’s gene pool. Thus along with the demographic changes that characterize contemporary human populations has come the expression of traits that increase morbidity and mortality in later life, but that were of relatively little consequence when large numbers of individuals died before the completion of reproductive life. Moreover, relatively low efficiency of calcium absorption and highly effective mechanisms for the mobilization of calcium during repro-
ductive life are beneficial traits early in life, especially for women, but become deleterious when other age-related, physiological changes upset homeostatic balance. In this sense, osteoporosis may be the expression of an antagonistic pleiotropy that is maintained in the human genome by selective advantage. If this is the case, success in preventing and treating osteoporosis will require modern medicine to prevail over evolution—a tall order perhaps, but in view of the recent history of biomedical technology, not an unattainable one.

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