

## Osteoporosis: Trends and Intervention

ANGELA M. INZERILLO, M.D.<sup>1</sup>, AND MONE ZAIDI, M.D., PH.D.<sup>2</sup>

### Abstract

Osteoporosis is a skeletal disorder in which bone strength is compromised due to loss of bone density and bone quality. It is the leading cause of serious morbidity and functional loss in the elderly. At times, it is difficult for the clinician to distinguish between the disease and normal skeletal aging, but advances in the scientific understanding of the underlying disease process have made management of osteoporosis a preventable disease for the most part. Defining the point at which these age-related skeletal changes require intervention presents a major challenge to researchers and clinicians alike. There are several reasons for these difficulties. There is a long period of bone loss before the onset of clinically apparent disease. Also, although current diagnostic procedures can distinguish those at risk of fracture and those not at risk, there is a large overlap in bone density between persons who experience fractures and those who do not. Research efforts directed at these issues have increased dramatically, as have developing technologies in the measurement and screening of bone mineral density. Ongoing advances in the therapeutic modalities have promoted new methods to treat this disorder.

This review will describe the mechanisms responsible for osteoporosis and the modalities used to screen and diagnose this common disorder. Various therapeutic approaches now in use, and some promising experimental trials, will be discussed.

**Key Words:** Bisphosphonates, bones, bone remodeling, calcium, DEXA, fracture, estrogen, osteoporosis, postmenopausal osteoporosis.

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### Introduction

OSTEOPOROSIS IS CHARACTERIZED by low bone mass as well as microarchitectural deterioration of bone, with a consequent increase in bone fragility and susceptibility to fractures (1). It is the leading cause of serious morbidity and functional loss in the elderly. Progress in the scientific understanding of the underlying disease process has made it, for the most part, a preventable disease. Rapidly developing advances in bone mass measurement and therapeutic modalities have allowed us to recognize and treat this disorder.

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From the Mount Sinai Bone Program, Department of Medicine, Division of Endocrinology, and Department of Geriatrics, Mount Sinai School of Medicine, New York, NY; and Bronx Veterans Affairs Geriatrics Research Education and Clinical Center, Bronx, NY.

<sup>1</sup>Instructor and <sup>2</sup>Professor of Medicine and Geriatrics.

Address correspondence to Mone Zaidi, M.D., Ph.D., Box 1055, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

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### Epidemiology of Osteoporosis

Osteoporosis is the most commonly occurring bone disease, and it is anticipated that the prevalence of osteoporosis will increase as the population ages (2). Ten million people in the United States have osteoporosis at the hip and nearly 18 million more have low bone mass at the hip. In the United States alone, the occurrence of osteoporotic fractures is even more striking, approximating 1.5 million per year. One in two women and one in eight men over age 50 will have an osteoporotic fracture (3).

The prevalence of low bone mass increases with increasing age in both men and women, reflecting age-associated bone loss. It is higher for women than men because accelerated bone loss occurs in the immediate postmenopausal period (4). Another difference between men and women is that men achieve a higher peak bone mass than women. Low bone mass is also more prevalent in Caucasians than in blacks (4).

When compared with other common chronic diseases in the United States, the data appear even more dramatic. For white women older than age 65, the incidence of hip fracture is greater than the incidence of stroke, breast

cancer and diabetes (5). Among other chronic ailments, 28 million are affected with osteopenia and osteoporosis, compared with 52 million and 42 million affected with hypercholesterolemia and hypertension, respectively (6).

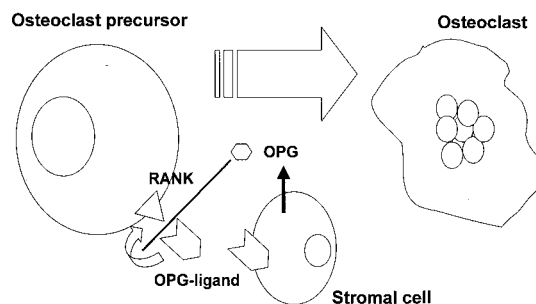
The economic toll that osteoporosis places on society is remarkable. The cost of all fractures in the United States is between \$35 and 41 billion per year. The cost of all osteoporotic fractures totals between \$10 and 15 billion per year. Hip fractures alone total between \$4 and 6 billion per year (7). Projected costs for all fractures for the year 2025 are \$64 billion (8).

### Bone Remodeling

In order to understand the pathophysiologic events underlying osteoporosis, it is essential to be aware of the processes involved in normal bone metabolism. Bone undergoes a continuous process of remodeling. Osteoporosis results from defective remodeling. Bone is resorbed by osteoclasts and is formed through the action of osteoblasts. Osteoblasts, formed from pluripotent precursors (which also form adipocytes and fibroblasts), lay down bone matrix (or osteoid) that ultimately becomes mineralized. The cells can either undergo apoptosis, or become buried into the matrix they form and become osteocytes. The latter are transducers of mechanical loading. Osteoblasts express receptors for estrogen and vitamin D in their nucleus, as well as integrin and cytokine receptors on their surface. Endogenous stimulants of osteoblastic activity include fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and transforming growth factor- $\beta$  (TGF- $\beta$ ).

Osteoclasts, derived from hematopoietic progenitor cells, are giant multinucleated cells found alone or in clusters. Receptor activator of nuclear factor-kappa B (NF- $\kappa$ B) ligand (RANKL), or osteoprotegerin-ligand (OPG-L), is now considered to be the single most important cytokine that is both necessary and sufficient for bone formation (Fig. 1) (9). It is expressed on committed preosteoblastic precursors and T lymphocytes. In addition, a variety of other factors modulate osteoclast formation at various stages. These include interleukin-1 (IL-1), IL-3, IL-6, IL-11, tumor necrosis factor (TNF), vitamin D<sub>3</sub>, granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) (10).

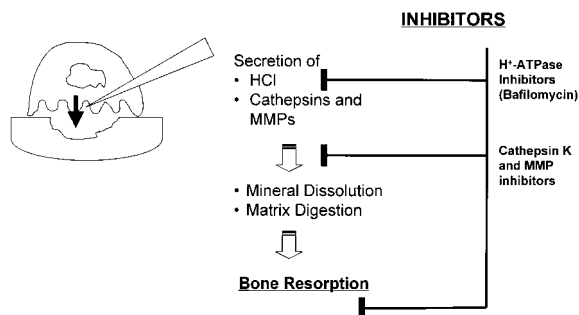
To resorb bone, osteoclasts attach to the endosteal bone surface and create a tight seal of



**Fig. 1.** Discovery of the osteoprotegerin control system. OPG = osteoprotegerin; RANK = receptor activator of nuclear factor-kappa B

close adhesion between their ventral surface and the bone matrix (Fig. 2). Osteoclasts secrete acid through a proton pump system that solubilizes the hydroxyapatite crystals and exposes the protein matrix. Digestive enzymes such as cathepsins and metalloproteinases (MMPs) then dissolve the protein matrix and liberate previously deposited growth hormones and collagenases. Thus, the resorptive process includes osteoclast formation from its precursor, polarization with creation of a ruffled border, induction of resorption through acidification and release of enzymes, resulting in the release of molecules from the matrix, and finally apoptosis of the osteoclast.

Once resorption is completed, the resorptive cavity becomes refilled with osteoblasts that initiate formation. In a repeating cycle of events, bone resorption is closely coupled to bone formation. The signal that couples bone resorption with subsequent bone formation is unknown. However, when there is either enhanced osteoclastic activity or decreased osteoblastic activity, each resorption cavity is only partially filled, resulting in net bone loss.



**Fig. 2.** Resorption by mature osteoclasts. MMP = metalloproteinase.

### Defining the Types of Bone Loss

As previously mentioned, bone loss occurs when the processes of formation and resorption become decoupled. There may be absolute osteoclast overactivity (possibly with increased numbers of osteoclasts) in high-turnover osteoporosis, as occurs in postmenopausal osteoporosis (Table 1). Bone remodeling is enhanced, with a disproportionate increase in resorption, resulting in accelerated bone loss. The exact cellular mechanism by which estrogen withdrawal after menopause exerts its effect on osteoclast formation and function is not entirely known. Certain osteoclastogenic and resorptive cytokines, such as IL-6 and M-CSF, are upregulated, leading to enhanced osteoclast formation and activity, which then results in bone loss.

In low-turnover osteoporosis, such as that which occurs with aging, bone formation lags behind resorption; thus, the rate of resorption exceeds that of formation, resulting in net bone loss. There is a primary defect in osteoblastic activity as well as decreased bone formation. The precise cellular details remain unclear. Another hypothesis is that bone loss, even in men, is caused by reductions in the level of estrogen that occur with aging.

Secondary osteoporosis, which is osteoporosis due to conditions other than aging or menopause, may arise from a variety of causes. When patients have unexplained bone loss, laboratory evaluation should be performed to determine if secondary causes may be superimposed on primary bone loss. If laboratory evaluation is negative, a bone biopsy may provide useful information. Common causes of secondary osteoporosis are listed in Table 2.

### Predictors of Low Bone Mass and Fractures

Identifying those at risk for osteoporosis and fractures is important in the clinical management of patients. Studies reveal that risk factors for osteoporosis predict fracture, but

these risk factors do not predetermine the extent of bone mineral density (11, 12). According to the 1998 National Osteoporosis Foundation (NOF) Guidelines, family history, age, history of fracture, smoking, female sex, Caucasian race, estrogen deficiency, and low body weight are risk factors for the development of osteoporosis (13). Smoking poses a major risk for the development of osteoporosis, increasing the relative incidence of hip fracture by 1.5–2.0-fold (14). The same is the case with calcium intake below the recommended daily allowance (15). Other risk factors associated with hip fracture are maternal history of hip fracture, past fracture, particularly after age 50, anticonvulsants, hyperthyroidism and others (Tables 2 and 3).

It is now clear that low bone mass predicts fracture risk (16–18). For every standard deviation decrease in bone density measured at any site, the odds ratio for a fracture at any site is 1.6–2.4 (19). This relationship holds for both men and women (19). A combination of low bone density plus one or more prior vertebral fractures increases relative risk of fracture by 2.5-fold (19). The risk of fracture increases progressively and exponentially with decreasing bone density.

### Diagnosis

The diagnosis of osteoporosis can be made clinically, radiographically or by measurements of bone density (Table 4). As explained earlier, bone mass measurements have now been shown in multiple prospective studies to accurately predict fracture risk (16–18). The gold standard for the measurement of bone density is the Dual Energy X-ray Absorptiometry (DEXA).

The World Health Organization (WHO) has defined osteoporosis in terms of bone mineral density in postmenopausal Caucasian women. A bone density measurement of more than 2.5 standard deviations below the mean for young adult women without a history of fractures, using DEXA of the spine, hip, or forearm, con-

**TABLE 1**  
*Osteoporosis*

<b>Involutional</b>	<b>Postmenopausal</b>	<b>Secondary</b>
Remodeling is normal or decreased	Remodeling is elevated	Etiology-dependent changes in remodeling
Formation < resorption	Formation > resorption	
Osteoblastic defect	Osteoclastic defect	

**TABLE 2**  
*Secondary Causes of Osteoporosis*

<b>Endocrine</b>	<b>Gastrointestinal</b>	<b>Drugs</b>	<b>Genetic &amp; Other</b>
Hypogonadism	Alcohol	Anticonvulsants	Osteogenesis imperfecta
Cushing's syndrome	Malabsorption	Heparin	Homocystinuria
Hyperthyroidism	Celiac disease	Glucocorticoids	Marfan's syndrome
Type 1 diabetes	Crohn's disease	FK 506	Rheumatoid arthritis
Hyperparathyroidism	Lactase deficiency	Thyroid suppression	Ehler-Danlos syndrome
	Hepatic failure	Vitamin A excess	
<b>Malignancy</b>	Low vitamin D intake	Methotrexate	<b>Renal Disease</b>
Multiple myeloma	Anorexia nervosa	Cyclosporin A	Renal failure
Lymphoma	Gastrectomy	Alcohol	RTA
Leukemia	Small bowel resection		Idiopathic hypercalciuria
Malignancy- induced PTHrP secretion		<b>Immobilization</b>	
Mastocytosis	<b>Lifestyle</b>	Hip fracture	
	Smoking	Paralysis	

PTHrP = parathyroid hormone-related protein; FK506 = tacrolimus; RTA = renal tubular acidosis

**TABLE 3**  
*Risk Factors for Osteoporotic Fractures*

Age	Anticonvulsant therapy
Female sex	Hyperthyroidism
Caucasian race	Alcoholism
Low bone density	Excess dietary protein
Prior fracture after age 50	Family history
Hypogonadism	Inactivity
Smoking	Corticosteroids
Falls	

stitutes a diagnosis of osteoporosis (20). Note that this criterion identifies approximately 30% of postmenopausal women as having osteoporosis. It approximates an equivalent lifetime risk for spine, hip and forearm of about 17% and lifetime fracture risk for any of the three sites of about 40% (20).

### Commonly Used Techniques

#### Dual Energy X-Ray Absorptiometry

DEXA utilizes a beam of x-ray photons passing through the bone region of interest.

This technique measures the sum of cortical and trabecular bone at the mid-radius (95% cortical bone), lumbar spine, femoral neck, total hip and total body, with a precision of approximately 1–3% (21). Radiation exposure is low (1–3  $\mu$ Sv per site) and patient acceptability is high. For the sake of comparison, radiation exposure from a chest x-ray ranges from 50–150  $\mu$ Sv, where 1 Sv (Sievert) equals 100 rem.

Potential uses of bone densitometry include screening of asymptomatic persons to assess their risk of future fracture, diagnostic density measurements of persons with known risk factors for osteopenia, and repeat measurements for purposes of following bone mass changes over time, in response to disease or antiresorptive treatments (22).

Measurement of at least two skeletal sites, usually lumbar spine and hip, is preferable. It is important to recognize falsely elevated bone mineral density on DEXA when interpreting results. Reasons for such artifacts include degenerative joint or disk disease, compression fractures, vascular calcifications, or scoliosis. Use of femoral neck, total hip and forearm as well as a lateral vertebral assessment measurement is usually preferable under these clinical circumstances (21).

**TABLE 4**  
*Osteoporosis Diagnosis*

Clinical	Radiological	Markers
Height loss	DEXA	OH-proline (hydroxyproline)
Kyphosis	Spinal CT	
X-ray finding	pCT	N- and C- telopeptide
Fracture	$\mu$ CT	Collagen crosslink peptides
Acute crash syndrome	MRI	
	Ultrasound	

MRI = magnetic resonance imaging

DEXA = dual energy x-ray absorptiometry

spinal CT = spinal computerized tomography

pCT = peripheral computerized tomography

$\mu$ CT = microcomputerized tomography

DEXA values are reported by comparison to age- and gender-reference groups, with T scores (standard deviations above or below values for young normals) and Z scores (standard deviations above or below age-matched values) (21). A T score more than 2 standard deviations below young normals indicates an increased risk of fracture, and should lead to consideration of antiresorptive therapy to prevent further bone loss, according to the National Osteoporosis Foundation. A Z score of more than 1–2 standard deviations below the age-matched mean value should prompt a thorough evaluation for secondary causes of bone loss (Tables 2 and 3).

### Quantitative Computed Tomography (QCT)

Vertebral bone densitometry by quantitative computed tomography (QCT) is an attractive alternative to DEXA. This is the only method available that can separately quantitate cortical and trabecular bone, and can potentially detect the signs of bone loss which first occurs in the trabecular skeletal compartment. It allows volumetric bone mineral density (BMD) measurement, and it is useful in degenerative disease in the spine and individuals at extremes for size and weight. However, radiation dose per scan is also substantial and patient acceptability is limited. DEXA is generally preferable to QCT in terms of precision, accuracy, radiation exposure, quality control, and logistics in the clinical radiology setting (21).

### Peripheral Measures

Compared to central DEXA, peripheral DEXA and peripheral QCT are performed using smaller, portable units which are easier to operate and emit less radiation. They also require

shorter scan times, and decreased cost makes them particularly suitable for screening. Sites measured include the radius, calcaneus and phalanges. Because different normative databases are utilized, these methods are not utilized for serial measurements.

Newer measures of bone strength, such as ultrasound, have been introduced. Currently, only peripheral sites can be measured, including radius, phalanges, calcaneus, and tibia.

### Other Modalities

Advances in bone density measurement include lateral vertebral assessment (LVA) which is performed by DEXA as well as magnetic resonance imaging (MRI), and microcomputerized tomography ( $\mu$ CT). These techniques demonstrate actual bone morphology as a measure of bone "quality" through an interpretable digital image. In contrast, DEXA merely provides quantitative information on bone mineral density.

### Screening Guidelines

The National Osteoporosis Foundation has recommended densitometry for menopausal women whose decisions regarding estrogen replacement therapy would be influenced by knowledge of bone mass (13). Other recommended indications for densitometry are given in Table 5. These include densitometry in patients with radiographic evidence of osteopenia, patients on chronic glucocorticoids or with other conditions such as asymptomatic primary hyperparathyroidism where knowledge of bone density will influence management (21, 22).

Peripheral measurements of bone density are now being used more frequently for screening. They are useful for screening because of

**TABLE 5**  
1998 National Osteoporosis Foundation (NOF)  
Recommendations for BMD Testing

1. All postmenopausal women under age 65 who have one or more additional risk factors for osteoporosis (besides menopause).
2. All women age 65 and older regardless of additional risk factors.
3. Postmenopausal women who present with fractures.
4. Women who are considering therapy for osteoporosis, if BMD testing would facilitate the decision.
5. Women who have been on hormone replacement therapy for prolonged periods.

Physician Guidelines to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 1998 and 2000. A copy may be obtained from the National Osteoporosis Foundation, 1232 22nd Street NW, Washington, DC 20037-1292 or <[www.nof.org/physguide/indep.htm](http://www.nof.org/physguide/indep.htm)>

their low cost, as well as their lack of ionizing radiation and their portability. However, results are difficult to interpret, because different normative databases are utilized and T scores do not correspond to the WHO criteria applicable to central DEXA measurements.

#### Serial Measurements to Assess Bone Loss Rates

Serial densitometries are helpful in determining whether patients need treatment if they have normal baseline bone mass but might otherwise be at risk for rapid loss, as in the immediate postmenopausal period or with the initiation of glucocorticoid therapy. Similarly, assessment of effectiveness of therapy in persons undergoing treatment may benefit from information on bone mass changes over time.

Currently, the only serial measurements that have been substantiated are the ones utilizing DEXA. At present, the available methods are sufficiently precise for measurement of bone mass changes if multiple measurements are taken or expected changes in bone mass are large. For patients undergoing treatments that are expected to produce large (>10%) losses or gains of bone mineral density, serial measurements may help identify nonresponders or patients requiring a change in therapy. Serial measurements over relatively short intervals are not useful in assessing bone mass response to preventive measures such as estrogen replacement, because expected rates of change are small by comparison with the precision variability of the technique.

#### Biochemical Markers of Bone Turnover

Biochemical markers of bone turnover are a useful adjunct in the management of osteoporosis. High bone turnover, which can be measured by biochemical markers, is an independent predictor of increased fracture risk (23–27). Biochemical markers are useful in assessing rapid bone loss as well as risk of fracture, and in monitoring therapy (28). Common markers of bone formation available for clinical use include alkaline phosphatase, bone-specific alkaline phosphatase and osteocalcin. Resorption markers include pyridinoline, hydroxyproline, deoxypyridinoline, and N- and C-telopeptides. The latter are collagen breakdown products that enter the circulation following bone resorption. Their clinical usefulness in individual patients needs to be determined (28).

#### Prevention and Treatment of Osteoporosis

Osteoporosis therapy ideally should be aimed at the underlying type of osteoporosis, i.e., involuntional, postmenopausal or from secondary causes. The majority of agents available today are antiresorptives that exert the most beneficial effect in those types of osteoporosis with a high rate of bone turnover. See Table 6 for a complete listing of treatment modalities.

#### Calcium

Multiple placebo-controlled studies (29, 30) have demonstrated the importance of adequate calcium intake for both primary and secondary prevention of osteoporosis. Chronic deficiency inevitably leads to skeletal demineralization

**TABLE 6**  
Osteoporosis Therapy

Decrease Resorption	Enhance Formation
Estrogen and SERMs	Parathyroid hormone
Bisphosphonates	Vitamin D analogues
Calcitonins	Fluoride
New osteoclast-inhibitory agents	New osteoblast-stimulatory agents
	Exercise

SERMs = selective estrogen receptor modulators

and enhanced fracture risk (29). The effects of calcium supplementation are maximized in patients in whom baseline intake is low, especially in the elderly (29). Premenopausal and menopausal women, as well as middle-aged and older men and frail female nursing home residents, respond to calcium supplementation with small to modest increases in bone mineral density (30–34). Women in early menopause, presumably because of the dominant effect of gonadal hormone loss, do not show such an effect (29, 30). These data suggest that the use of calcium and vitamin D supplementation should be routine, but must be combined with antiresorptives or bone-forming therapies.

The 1994 Consensus Development Conference on Optimal Calcium Intake advised that the recommended daily allowance (RDA) for calcium be increased in most age groups, particularly in childhood and in adolescence, when 40% of total adult bone mineral is formed. Total, i.e., diet plus supplemental, intakes of 1.5–2.0 g of 'elemental' calcium per day are recommended for postmenopausal women (34), although intake must be individualized.

### Exercise

It is evident from multiple studies that immobility and disuse leads to accelerated bone loss. Active individuals have higher bone mass than inactive individuals (35), as has been shown in several cross-sectional studies. Correlations have been shown between muscle mass and bone density. For example, athletes have higher bone mass in skeletal regions of greatest exertion, and some prospective controlled studies in menopausal women have demonstrated increases in bone mass, total body calcium, and improved calcium balance in the exercising groups (35, 36). It is also clear that exercise is less critical than gonadal hormone sufficiency in the prevention of bone loss. Excess weight loss in premenopausal female marathoners leads to amenorrhea, bone loss, and fractures (37).

Questions regarding timing, age at onset, frequency, duration, and type of exercise most beneficial to maintaining bone remain to be answered. Many have proposed that the principal benefit of exercise in reducing fracture risk is its enhancement of muscle strength, balance and coordination, and an associated reduction in the risk of falls (38). General recommendations for exercising include: 30 minutes per day, 5–6 days per week; maintenance of a high level

of activities of daily living; and adaptation according to the individual's age, lifestyle, strength and agility. Exercise protocols must be individualized for patients and must be appropriate for their bone density.

### Estrogen

At the cellular level, estrogens bind to nuclear receptors present in both osteoblasts and osteoclasts (39–43). Estrogen acts on osteoblasts to produce a spectrum of different effects, including enhanced pro-collagen production, and increased alkaline phosphatase expression (41–45). Estrogen also modulates the synthesis of certain growth factors and cytokines.

Estrogen deficiency causes increased osteoclast formation by enhancing, among other effects, the phosphorylation of the nuclear protein, Egr-1, resulting in an increased production of the osteoclast-forming cytokine, M-CSF, from supporting stromal cells (46). Thus, the availability of estrogen inhibits osteoclast formation. Additionally, estrogen inhibits transcription of the gene for an osteoclast-forming molecule, RANKL (receptor activator for NF $\kappa$ B-ligand) (47). Therefore, in addition to modulating molecules like M-CSF, osteocalcin, osteonectin, and osteopontin, estrogen can directly suppress RANKL-induced osteoclast differentiation and thus bone resorption.

Inhibition of bone resorption by estrogen is evident clinically. When estrogen replacement therapy is initiated early in menopause (i.e., within the first 5 years) and continued for at least 10 years, hip fracture incidence is reduced by 50% (48–52), and significant reductions in distal radial and vertebral fracture also occur. Hormone therapy for preventing bone loss should therefore begin as soon after menopause as possible, in order to inhibit this accelerated loss that ensues within years 4 and 6. When estrogen is given during this phase, some patients may in fact gain new bone, as bone formation during this phase of intense remodeling can transiently exceed bone resorption (49). Thereafter, bone mass is stabilized or the rate of loss is slowed until treatment is discontinued, whereupon rapid loss once again begins. Thus, while estrogen therapy should be given indefinitely, theoretically, every year of use delays the onset of clinically important osteopenia, as demonstrated by the reduced hip fracture incidence seen in elderly women previously treated

with hormone replacement (49). In women with established bone loss, estrogen replacement has been shown to increase bone mass slightly, by a few percent over a 3-year period (53, 54). Estrogen also has other benefits, a discussion of which is beyond the scope of this review.

Despite the current knowledge of potential benefits of estrogen in inhibiting bone loss, many women discontinue treatment within one year due to side effects such as vaginal bleeding, and more commonly, fears of breast cancer and thrombosis (55, 56). Large-scale, prospective, randomized studies are required to clarify the ultimate effect of menopausal hormone replacement on overall morbidity and mortality, coronary heart disease, breast and uterine cancer, and osteoporotic fracture. Physicians and patients alike must balance the risk of osteoporosis and coronary heart disease against the risk of breast cancer in deciding for or against menopausal hormone replacement.

### Selective Estrogen Receptor Modulators

An important advance in osteoporosis treatment is the development of selective estrogen receptor modulators (SERMs) such as raloxifene, tamoxifen, and droloxifene. Raloxifene has been shown to bind with high affinity to estrogen receptors differently than estrogen, SERMs can confer a conformation that enables the receptor to interact with a different second messenger. Thus, raloxifene is an estrogen agonist for bone and lipoproteins, but an estrogen antagonist at the breast and uterus. Its mechanism of action in bone may involve the up-regulation of transforming growth factor  $\beta_3$  expression, thus inhibiting osteoclast formation and bone resorption (57, 58).

The clinical effects of raloxifene on BMD and antifracture efficacy have been shown by a number of prospective placebo-controlled trials. Studies have demonstrated a BMD increase of 2.4% at the spine and the hip at three years (59) and a significant reduction, about 30–50%, in vertebral fractures (60). Additional benefits of raloxifene include its favorable lipoprotein profile and a 76% reduction in invasive breast cancer (61). Its side effects include venous thromboembolism and lack of relief of postmenopausal vasomotor symptoms. More long-term studies are needed to evaluate hip fracture efficacy as well as possible side effects on the uterus and breast.

### Calcitonin

Calcitonin is a 32-amino-acid peptide hormone synthesized and secreted from the C cells of the thyroid. It is a potent inhibitor of osteoclastic bone resorption and acts on a G protein-coupled receptor in the osteoclast. It triggers both cyclic AMP and calcium pathways to cause osteoclast inhibition (62).

Several prospective controlled trials with calcitonin have also documented stabilization of, and in some cases modest short-term increases in, bone mass in osteoporotic patients treated for 5 years or less (63–65). Similar effects have been demonstrated utilizing calcitonin as a preventive treatment for menopausal trabecular bone loss (65, 66). Studies directly evaluating the impact of calcitonin on fracture rate reduction have all shown that rate to be reduced significantly, together with modest increases in BMD (67–70).

Compromised trabecular microarchitecture is an important and independent causal factor in the pathogenesis of vertebral fractures in both men and women (71). It is now emerging that there is a temporal dissociation between reduction in fracture risk, which can occur in 12–18 months, bone markers and long-term effects on BMD. Notably, a benefit in fracture risk occurs before a change in BMD. Recent clinical trials with antiresorptives, such as calcium plus vitamin D, calcitonin, and raloxifene, indicate significant protection from fracture despite only modest increases in BMD. This has led to the belief that by preventing osteoclastic resorption, antiresorptives, such as calcitonin, conserves bone microarchitecture (72).

### Bisphosphonates

Bisphosphonates (BPs) are stable analogs of pyrophosphate that inhibit bone resorption. Their main effects include decreased osteoclast progenitor development, decreased osteoclast recruitment, and induction of osteoclast apoptosis, leading to inhibition of bone resorption (73–75).

Alendronate sodium, a second-generation aminobisphosphonate, has been used for the prevention and treatment of postmenopausal osteoporosis, glucocorticoid-induced osteoporosis and male osteoporosis. Clinical trials demonstrated significant reductions in both vertebral and nonvertebral fractures (76), in association with significant gains in bone mineral density (77), including BMD increases of 8.8%

in the spine and 5.9% in the femoral neck. Its use was associated with a 48% decrease in vertebral fractures (78).

A new bisphosphonate, risedronate sodium, which is a potent third generation bisphosphonate, was recently approved by the FDA for the prevention and treatment of postmenopausal osteoporosis, and for the prevention and treatment of glucocorticoid-induced osteoporosis in men and women.

There is an association between alendronate and erosive esophagitis. Patients often discontinue taking this drug if they experience nausea, dyspepsia and other nonspecific gastrointestinal side effects which usually predate the esophagitis. Recent short-term studies reveal similar increases in BMD with once- and twice-weekly dosing of alendronate in order to minimize gastrointestinal side effects and maximize compliance (79, 80). Long-term efficacy studies are needed to document fracture efficacy.

### Other Treatments for Osteoporosis

#### Sodium Fluoride

Fluoride stimulates new bone formation by increasing osteoblastic activity. Bone biopsies demonstrate increased trabecular volume, thickness and osteoid surfaces. Initially, the new bone formed may be poorly mineralized woven bone, but it is eventually replaced by a lamellar bone structure. Prospective, controlled clinical trials have demonstrated linear increases in spine and hip bone mass, but decreased radial cortical bone mass (81, 82). No significant decreases in vertebral fractures rates were observed in these studies, but there was a significant increase in the number of nonvertebral fractures at sites high in cortical bone (81, 82). This suggests that fluoride may cause formation of new trabecular bone, but not of appendicular cortical bone. At this time, the slow-release sodium fluoride formulation is not commercially available in the United States. Because of its substantial side effects, fluoride is best used only in clinical trials.

#### Parathyroid Hormone

Parathyroid hormone (PTH) acts on osteoblasts to modulate the expression of a variety of growth factors, including IGF-1, TGF- $\beta$ 1 and TGF- $\beta$ 2, as well as certain cytokines (83, 84). The precise mechanism underlying the anabolic effects of PTH on bone is just beginning

to be understood. When administered intermittently, at a low dose, PTH stimulates bone formation (Table 7). Several clinical trials have demonstrated increases in bone mass and volume with low, intermittent doses of PTH (85, 86). Promising data obtained from a recent multicenter clinical trial revealed that daily injections of parathyroid hormone (1-34) at doses of 20  $\mu$ g and 40  $\mu$ g, compared to placebo, increased the bone mineral density of the spine by 9 and 13 % respectively, and at the femoral neck by 3 and 6 % respectively. The risk of new vertebral fractures was reduced by 65 and 69 percent respectively, as compared with placebo (87). The major drawback of PTH administration is that it must be administered parenterally to achieve the pulsatile increases in the serum necessary to enable bone formation.

### Vitamin D and Vitamin D Analogs

Aging is associated with decreases in intestinal calcium absorption, calcitriol levels and responsiveness of the 1-hydroxylase enzyme to parathyroid hormone stimulation. While vitamin D may indirectly stimulate bone resorption, it also enhances gastrointestinal calcium absorption, promotes mineralization, and inhibits PTH-induced bone resorption.

Results from clinical trials of calcitriol (1,25 dihydroxyvitamin D) have been contradictory. Its use has been associated with an increased risk of hypercalcemia and hypercalciuria, necessitating regular monitoring of calcium intake and serum as well as 24-hour urinary excretion of calcium. Pharmacologic doses of vitamin D metabolites, therefore, cannot be recommended routinely. However, the use of physiologic doses of vitamin D (800 IU per day) has demonstrated efficacy in reducing fracture rates in the elderly, and should now be consid-

**TABLE 7**  
*New Bone-Forming Agents*

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Parathyroid hormone analogues
Calcilytics (Ca <sup>2+</sup> receptor antagonists)
Bone morphogenetic proteins
Growth factor and growth factor binding protein modulators (IGF and TGF- $\beta$ )
Vitamin D analogues
Prostanoids

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ered as standard regimen. While new vitamin D analogues, which carry a decreased risk of hypercalcemia, have been introduced, there are no long-term studies evaluating their use in the prevention or treatment of osteoporosis.

### HMG-CoA Reductase Inhibitors

Recent animal studies have shown that the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase by the lipid-lowering statins activate osteoclast apoptosis and reduce osteoclast recruitment, as well as promote osteoblastic bone formation. *In vitro* and *in vivo* evidence has led to the findings that aminobisphosphonates inhibit the biosynthetic pathway from mevalonate to cholesterol, resulting in osteoclast apoptosis. Statins act on the same pathway upstream of bisphosphonates in osteoblasts and enhance the expression of bone morphogenic protein-2 (BMP-2), an important osteoblast differentiation agent. It is thought that BMP-2 upregulation mediates the bone-forming effect of statins.

Promising clinical studies have become available. One retrospective trial involving patients with type 2 diabetes mellitus revealed significant increases in BMD at the spine and the hip in those patients treated with lovastatin, pravastatin, or simvastatin compared to controls (88). Other retrospective studies document a decreased fracture risk in those treated with statins (89, 90). Further controlled, prospective clinical trials are necessary to determine the clinical applicability of statins to osteoporosis treatment.

### Other Treatment Strategies

Potential development of bone-forming agents includes growth factors (insulin-like growth factors I and II, and transforming growth factor  $\beta$ ), parathyroid hormone analogues, and bone morphogenic proteins which mediate their effects through proliferation of osteoblasts and are currently undergoing evaluation for methods of localizing their effects to the skeleton (Tables 7 and 8).

### Conclusion

Through advances in the scientific understanding of bone remodeling, new clinical measures of bone mass, and access to more therapeutic modalities, powerful tools are now available to detect and treat osteoporosis, a dis-

**TABLE 8**  
*New Osteoclast Inhibitory Agents*

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Small molecule modulators of osteoclastogenic cytokines and their receptors
Ca <sup>2+</sup> receptor agonists
H <sup>+</sup> -ATPase inhibitors
Integrin receptor modulators
Calcitonin receptor mimics
Nitric oxide donors
Osteoprotegerin (OPG)

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ease physically disabling and financially draining. More work needs to be done in order to identify potential therapeutic agents that can increase bone formation. New and better techniques are needed to measure bone strength. With ongoing research, osteoporosis should come to be considered a preventable and curable disease.

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