



## Osteoporosis in elderly: prevention and treatment

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Osteoporosis is a common disease of older adults and is a major public health problem worldwide. As the population ages, the incidence of osteoporosis and resulting osteoporotic fractures is increasing. Although osteoporosis is more common in women than in men, the incidence in men is increasing. The disability, mortality, and cost of hip and vertebral fractures are substantial in the rapidly growing, aging population so that prevention and treatment of osteoporosis is a major public health concern. This article reviews the impact of osteoporosis and provides an evidence-based approach toward preventing and treating osteoporosis and its complications.

### Definition

The Consensus Development Conference statement in 1993 defined osteoporosis as “a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk” [1]. In 1994, the World Health Organization (WHO) established bone mineral density (BMD) measurement criteria allowing the diagnosis of osteoporosis before incident fractures [2] (Table 1). This practical definition is based on its major (known) risk factor: reduced bone strength or density and includes those individuals who are at a high risk but without fractures. Despite the use of a “bone mass” definition, it is important to realize that bone density is a single risk factor, measured at a single point of time. Other

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Table 1

Diagnostic categories for osteoporosis in postmenopausal women based on World Health Organization Criteria

Category	Definition by bone density
Normal	A value for BMD that is not more than 1 SD below the young adult mean value.
Osteopenia	A value for BMD that lies between 1 and 2.5 SD below the young adult mean value.
Osteoporosis	A value for BMD that is more than 2.5 SD below the young adult mean value.
Severe osteoporosis	A value for BMD more than 2.5 SD or below the young adult mean in the presence of one or more fragility fractures.

*Abbreviations:* BMD, bone mineral density; SD, standard deviation.

*Data from* Kanis JA, Melton LJ, Christiansen C, Johnson CC, Khaltaev N. The diagnosis of osteoporosis. *J Bone Miner Res* 1994;9:1137–41.

risk factors including age, life expectancy, bone loss, and bone turnover are other important considerations.

## Epidemiology

Few premenopausal women have osteoporosis; however, the prevalence increases with age because of the progressive loss of bone. In the United States, it has been estimated that up to 54% (16.8 million) of postmenopausal white women have low bone mass (T score of  $\leq -2.0$ ) and another 20% to 30% (6.9 million) have osteoporosis [3]. In the United States, the prevalence of osteoporosis increases from 15% in 50- to 59-year-old women to 70% in women aged 80 years. Epidemiologic studies in other countries have reported similar findings [4,119].

A fracture is considered to be osteoporotic (fragility fracture) if it is caused by relatively low trauma, such as a fall from standing height or less; a force which in a young healthy adult would not be expected to cause a fracture. Overwhelming evidence has shown that the incidence of fracture in specific settings is closely linked to the prevalence of osteoporosis or low bone mass. In a prospective study of 8134 women older than 65 years in age, Cummings et al showed that the women with BMD of the femoral neck in the lowest quartile have 8.5-fold greater risk of sustaining a hip fracture than those in the highest quartile [5]. Each 1 standard deviation decrease in femoral neck BMD increases the age adjusted risk of having a hip fracture 2.6-fold. Thus, a strong correlation exists between BMD and fracture risk.

### *Hip fractures*

The incidence of hip fractures increases dramatically with age and typically peaks after 85 years of age. In the United States, in 1991, there were 300,000 hip fractures. Most of these fractures (94%) occurred in people age 50 and older, and

most (55%) occurred in people age 80 and over [6]. According to a large US population-based study of hip fractures among older persons, the age-adjusted rate of hip fractures was highest among white women (8.07 per 1000), followed by white men (4.28 per 1000), black women (3.06 per 1000) and black men (2.38 per 1000) [7].

With increasing life expectancy worldwide, the incidence of hip fractures will rise exponentially with age, unless preventive efforts are undertaken [8]. In 1990, an estimated 1.65 million hip fractures occurred (1.2 million in women and 450,000 in men) worldwide [9,10], which is projected to increase to 6.3 million by the year 2050; of which 70% are expected to come from Asia, Latin America, the Middle East, and Africa. In the United States alone, hip fractures could total 840,000 in the year 2040 [11–13].

### *Vertebral fractures*

Although vertebral fractures are the most common osteoporotic fractures, less is known about their epidemiology because approximately two thirds are asymptomatic and go undetected and because of the lack of a standardized morphometric definition [14]. Most studies have shown that there is an exponential rise in the number of fractures with aging. In the European Vertebral Osteoporosis Study, the prevalence of vertebral deformity was 10% in men age 50 to 54 years, rising to 18% at age 75 to 79 years. In women age 50 to 54 years, the prevalence was only 5%; however, this rose to 24% at age 74 to 79 years [15]. Similar results were reported from other studies [14].

### *Peripheral fractures*

Distal forearm fractures almost always result from a fall on the outstretched arm. The incidence in women becomes evident at an earlier age than vertebral fractures, rising rapidly soon after menopause. In men, the incidence remains relatively constant between the ages of 20 and 80 years [12,13,16,17]. Fractures of the proximal humerus and shaft and distal femur have an occurrence pattern that resembles that of hip fractures: substantial age-related increases in rates among white women late in life and lower risks in men and blacks of either sex [16,18]. Pelvic fractures also increase exponentially with age. Most of these fractures (ie, 70% to 80%) appear to result from minimal trauma, suggesting underlying osteoporosis.

## **BMD assessment methods**

### *Bone densitometry*

Bone densitometry is an established method for assessing osteoporosis. A variety of different methods have been developed over the past 25 years. The two most commonly used methods are dual energy x-ray absorptiometry (DEXA) and

quantitative ultrasound. DEXA is recommended and FDA approved for BMD measurement; it is precise, noninvasive, has low radiation exposure, and takes 10 minutes to administer. Because annual losses of bone mass normally seen with aging range from 1% per year, the precision error of current instruments (approximately 1% to 2% with DEXA) cannot provide reliable information at intervals shorter than 2 years. Therefore, if follow-up studies are desired, a minimum interval of 2 years is recommended. Exceptions to this include high-dose steroid therapy that can result in rapid bone loss in a shorter interval (6 to 12 months) The National Osteoporosis Foundation has published recommendations for BMD screening using DEXA [19] (Table 2). The cost of DEXA (approximately \$150 to \$250) is covered by Medicare.

### *Biochemical markers*

Despite the lack of definitive guidelines concerning biochemical markers, they have the potential to provide independent or adjunctive information on decision making [20,120]. Serum markers of bone formation include bone-specific alkaline phosphatase and osteocalcin. Markers of bone resorption are the collagen cross-links: deoxypyridinoline, N-telopeptide (NTx), and C-telopeptide (CTx). Although the resorption markers are measured in the urine, blood measurements have recently become available [21,22]. Women who have borderline low BMD and elevated markers are at increased risk of losing bone in the near future and may be candidates for pharmacologic intervention. The resorption markers are also independent risk factors for fracture.

### **Risk factors**

Risk factors for osteoporosis and osteoporotic fractures have been determined and are used to identify the need for further evaluation. Risk factors can be categorized as modifiable and nonmodifiable as represented in Table 3.

Table 2

National Osteoporosis Foundation recommendations for bone mineral density testing

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Postmenopausal women (age 50–65) with risk factors for osteoporosis (besides menopause)

- Family history of osteoporosis
- Personal history of low trauma fracture at age >45 yr
- Current smoking
- Low body weight (< 127 lb)

Women age 65 years and older regardless of additional risk factors

Postmenopausal women who present with fractures

Women considering therapy for osteoporosis if BMD testing would facilitate such a decision

Women who have been on HRT for prolonged periods

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*Abbreviations:* BMD, bone mineral density; HRT, hormone replacement therapy.

*Data from* National Osteoporosis Foundation. Osteoporosis: review of the evidence for prevention, diagnosis, and treatment and cost-effective analysis. Introduction. National Osteoporosis Foundation: Osteoporosis Int Suppl. 1998;S7–S80.

Table 3  
Risk factors for osteoporosis

Modifiable	Non-modifiable
Inadequate exercise	Age
Inadequate nutrition	Gender
Calcium	Race
Vitamin D	Early menopause
Smoking	Family history of fractures
Alcohol abuse	
Medications	
Glucocorticoids	
Benzodiazepines	
Anticonvulsants	
Thyroid hormones	

Although low BMD has been established as an important predictor of future fracture risks, several studies have shown that other risk factors also contribute to the fracture risk. In the Study of Osteoporotic Fracture (SOF) [23], clinical risk factors predictive of fracture were identified and were related to historical factors, such as previous fracture in the individual or her mother, self-rated poor health, use of long-acting benzodiazepines, and sedentary lifestyle; BMD; and physical examination findings, such as inability to rise from a chair; poor visual performance, and resting tachycardia. The presence of five or more of these factors increased the rate of hip fractures for women in the highest tertile of BMD from 1.1 per 1000 women-years to 9.9 per 1000 women-years, whereas for women in the lowest tertile, hip fractures increased from 2.6 per 1000 woman-years to 27.3 per 1000 woman-years. The Framingham Osteoporosis Study evaluated risk factors for bone loss in elderly men and women [24]. Data from this study suggested that for women, lower baseline weight, weight loss in the interim, and greater alcohol use were associated with BMD loss, while current estrogen users had less bone loss than nonusers. For men, lower baseline weight, loss of weight and smoking cigarettes were associated with BMD loss.

### Disability associated with osteoporosis

Osteoporosis can have a significant impact on the daily life of patients. Persons in whom osteoporosis is asymptomatic or has resulted in a single fracture can function well and usually do not experience substantial problems. When subsequent fractures occur, however, the functional outlook changes. Most of the persistent functional limitations result from fractures of the proximal femur or vertebrae.

#### *Outcomes with hip fracture*

Hip fracture mortality is higher for men than for women, increases with age, and is greater for those with coexisting illnesses and poor prefracture functional

status [6,25]. There are approximately 31,000 excess deaths within 6 months of the approximately 300,000 hip fractures that occur annually in the United States [6]. The mortality is higher in the elderly population—approximately 8% of men and 3% of women age 50 and older die while they are hospitalized for their fractures. At 1 year after hip fracture, mortality is 36% for men and 21% for women and is much higher in older men. Mortality rate returns to normal for the hip fracture population within 1 to 2 years; however, higher rates persist for the elderly [6,26].

Substantial long-term morbidity is associated with hip fractures. The proportion of US hip fracture patients who were discharged from hospital to nursing homes in 1990 varied from 14% for the youngest group (50 to 55 years) to 55% for those older than 90 years. One year after hip fracture, 40% of people were still unable to walk independently, 60% required assistance with one basic activity of daily living, and 80% were unable to perform at least one instrumental activity of daily living that they performed before fracture [6]. About one quarter of formerly independent people become at least partially dependent, half of those who already required assisted living were admitted to nursing homes, and those already in nursing homes remained there [6]. A French study of clinical outcomes after hip fractures also concluded that 20% of previously independent people required some form of assisted living arrangement after the hip fracture [27].

### *Outcomes with vertebral fracture*

Multiple cross-sectional and observational studies have found a positive correlation between vertebral fractures and back pain [28–30]. Vertebral deformity leads to loss of spinal mobility, and patients with osteoporosis have reported problems with standing, bending, rising from a chair, walking, carrying items, dressing, fixing hair, washing, bathing, moving in the bed, using the toilet, and getting to the floor [31–34]. Compared with women without existing vertebral deformities, those women with prevalent deformities have generally higher crude rates of mortality and hospitalization [35,36].

The pain and functional limitations that accompany vertebral fractures often cause a high level of anxiety early in the disease leading to inactivity and a sedentary lifestyle, thereby increasing the risks for falls and fractures and for fears of these events. As disease-related problems in the forms of additional vertebral fractures, pain, and limited mobility continue to appear, anxiety may transform into depression [31,32,37]. Both women and men living with progressive osteoporosis have decreased self-image and self-esteem because of feelings of worthlessness stemming from their inability to work outside the home, to enjoy hobbies, or to do chores around the house. Osteoporosis robs older women of many of their social roles. Inability to fulfill the roles such as cooking, housekeeping, working, and sexual intimacy can be devastating, leading to frustration and embarrassment [37]. Interpersonal relationships can be profoundly affected by effects of osteoporosis and can strain familial ties and destroy nonfamily relationships, leading to social isolation. Therefore, treatment options

for the affected individuals must focus not only on bone remodeling but also on ways in which adverse outcomes, such as pain, depression, and loss of self-esteem, can be improved.

### **Nonpharmacologic management**

Reduction of the potentially modifiable risk factors along with exercise and calcium and vitamin D supplementation form an important adjunct to pharmacologic management of osteoporosis.

#### *Exercise*

Physical activity may have a twofold contribution to reducing fracture risk: (1) it may enhance bone strength by optimizing BMD and improving bone quality and (2) it has the potential to reduce the risk of falling. Much of the data suggesting a relationship between bone strength (measured as BMD) and physical activity is cross-sectional, however, and cannot prove a cause and effect relationship.

Resistance training increases bone mass and prevents age-related declines in BMD [38–40]. A recent meta-analysis of the role of exercise showed that both impact and nonimpact exercise had a positive effect on lumbar spine bone density in postmenopausal women, whereas only impact exercise probably had a positive effect at the femoral neck [41].

The emphasis of physical exercise programs in elderly patients with osteoporosis should be on improving muscle strength and balance. Older patients should be encouraged to participate safely in any activity in a frequent, regular, and sustained manner. The exercise should be weight bearing and easy to complete and should fit into their daily routine. A program of walking, sitting, and standing exercises, or water aerobics, can be recommended to start with and gradually increased to more rigorous activity. For patients who have already had an osteoporotic fracture, physical exercise program can help reduce pain and increase functional capacity. The program should increase the patient's ability to perform routine daily activities while minimizing the risk of further fractures. For patients with vertebral fractures, back flexion exercises have been found to be harmful and to increase the risk of new vertebral fractures. These patients will benefit from resistance exercises that strengthen back extensor muscles [42].

#### *Calcium and vitamin D*

Deficiency of calcium and vitamin D contributes to alterations of bone remodeling and bone integrity. Low calcium intake and vitamin D deficiency have been repeatedly observed in the elderly population. In elderly women, low fractional calcium absorption in the setting of low calcium intake increases the risk for hip fracture [43]. Although vitamin D and calcium alone have little effect

on bone mass in the early menopausal years [44,45], they can have substantial effects on bone mass and fragility fractures in the elderly population.

In a 4-year randomized, double-blind, placebo-controlled trial of calcium citrate (1600 mg/d) or placebo in postmenopausal women (mean age, 66.3 years), patients in the calcium group lost significantly less bone at the lumbar spine ( $P = 0.003$  at year one) and proximal femur ( $P = 0.02$  at year one) as compared with the placebo [46]. In another randomized, double-blind, placebo-controlled trial of women older than 60 years of age with calcium intake of less than 1 g/d, supplementation with calcium carbonate 1.2 g/d decreased the rate of spinal fractures compared with placebo ( $P = 0.023$ ) and halted measurable bone loss [47]. To evaluate whether calcium supplementation can correct seasonal (winter-time) bone loss, 60 elderly women were supplemented with four glasses of milk each day, calcium carbonate (1000 mg/d), or a placebo [48]. After 2 years, the calcium group had no loss at the greater trochanter and had significant gains at the spine and femoral neck, whereas the placebo group had significant bone loss at the greater trochanter ( $P < 0.03$ ).

Few studies have evaluated the effects of vitamin D alone on bone mass and fractures. In a population of elderly Finnish men and women (mean age, 82.8 years), Heikinheimo et al [49] injected subjects with 150,000 or 300,000 IU vitamin D<sub>2</sub> once a year for 4 years. Fewer upper extremity and rib fractures were found in the group supplemented with vitamin D; however, no difference was noted in hip fractures. To evaluate the role of vitamin D in seasonal bone loss, women received a daily placebo or 400 IU vitamin D along with 377 mg/d calcium citrate [50]. Spinal bone loss in winter was less in the vitamin D-treated group than in the placebo group ( $P = 0.032$ ).

Two placebo-controlled trials have shown a significant protective effect against hip and other nonvertebral fractures by a combined supplement of calcium and vitamin D (Table 4). In a nursing home population, Chapuy et al [51] found that in the supplemented group, the parathyroid hormone (PTH) levels decreased by 44% from baseline, and serum 25-OH vitamin D levels increased by 162% over baseline. A 2.7% increase in BMD was noted in the proximal femur in the treatment group versus a 4.6% decrease in the placebo group ( $P < 0.001$ ) at 18 months. The supplemented group had 43% fewer hip fractures ( $P = 0.043$ ) and 32% fewer vertebral fractures ( $P = 0.015$ ) than the placebo group. In the trial involving ambulatory patients, Dawson-Hughes et al [52] found that dietary supplementation with calcium and vitamin D moderately reduced bone loss measured in the femoral neck, spine, and total body over the 3-year study period. Twenty-six patients in the placebo group and 11 patients in the calcium-vitamin D group had nonvertebral fractures ( $P = 0.02$ ).

Thus, calcium and vitamin D are useful adjunctive therapies in preventing and treating osteoporosis in the elderly even though it remains unproved that they prevent hip fractures in the ambulatory elderly population. Nevertheless, calcium and vitamin D supplementation should be recommended for all elderly individuals to preserve bone health with advancing age. The optimal effective dose of vitamin D is 400 to 1000 IU/d. The recommended dose of calcium for elderly

women and men is 1500 mg/d; women on hormone replacement therapy (HRT) need 1000 mg/d. The preferred source of calcium is dietary. Because the recommended dose of calcium and vitamin D usually is not obtained through diet alone, calcium and vitamin D supplementation is recommended.

### Pharmacologic management

The primary goal of an intervention is to reduce the risk of fracture. The evidence-based approach requires proof of efficacy from adequately powered randomized controlled trials in which fracture is the primary endpoint. Adequately powered randomized controlled trials with fracture as the primary endpoint exist for alendronate, raloxifene, risedronate, and calcitonin. For HRT, the evidence for antifracture efficacy is based mainly on observational data. Table 5 summarizes the medications available in the United States to manage osteoporosis.

#### *Bisphosphonates*

Bisphosphonates are compounds that bind avidly to hydroxyapatite crystals on bone surfaces and are potent inhibitors of bone resorption. The two bisphosphonates approved by the FDA are alendronate and risedronate.

#### *Alendronate*

Alendronate was the first bisphosphonate approved by the FDA (1995) to treat osteoporosis. In the phase III trial, almost 1000 postmenopausal women (mean age, 64 years) were randomized to alendronate or placebo for 3 years. Alendronate resulted in an increase in BMD of 8.8% in the lumbar spine and of 5.9% in the femoral neck as compared with placebo ( $P < 0.001$ ) [53]. Similar results were seen from two other trials [54].

The Fracture Intervention Trial (FIT) (Table 4) examined the effect of alendronate on postmenopausal women with low bone density at the hip and either with vertebral fracture at baseline (FIT I) or without vertebral fracture at baseline (FIT II). In the FIT I [55] trial, the rate of new radiographic vertebral fractures was decreased by 47% in the alendronate group compared with the placebo group ( $P < 0.001$ ). A similar reduction was also observed in the risk of hip and wrist fractures in women receiving alendronate: 51% reduction in hip fractures (95% CI 0.23 to 0.99) and 48% reduction in wrist fractures (95% CI 0.31 to 0.87).

In FIT II [56], alendronate did not reduce the risk of clinical fractures (RR = 0.86 [95% CI .73 to 1.01]  $P = 0.07$ ) in the entire cohort. In posthoc analysis, however, in women whose initial femoral neck T score was  $\leq -2.5$  or less, alendronate significantly reduced the risk of clinical fractures by 36% (RR = 0.64 [95% CI 0.50 to 0.82]) and hip fractures by 56% (RR = 0.44 [95% CI 0.18 to 0.97]). The pooled analysis of the FIT [57] concluded that the magnitude of the fracture reductions with alendronate are similar both in women who meet the

Table 4  
Selected clinical trials of drug treatment in management of osteoporosis

Author	Study design	Intervention	Population	Sample size	Results
Calcium and/or Vitamin D Chapuy et al [51] 1992	Randomized, placebo controlled	1200 mg calcium + 800 IU vitamin D	Healthy, ambulatory women (mean age, 84 yr) living in nursing home	I:1634 P:1636	32% fewer non vertebral fractures ( $P = 0.015$ ) 43% fewer hip fractures ( $P = 0.043$ )
Dawson-Hughes et al [52] 1997	Randomized, placebo controlled	500 mg calcium + 700 IU vitamin D3	Healthy, men and women (age $70 \pm 4$ yr) living in community	I:187 P:202	Significant increase in total body BMD ( $P < 0.001$ ) at second and third year Nonvertebral fractures I:11; P:26 ( $P = 0.02$ )
Recker et al [47] 1996	Randomized, placebo controlled	1200 mg calcium	Ambulatory elderly women (age $73.5 \pm 7.1$ yr) with calcium intake $< 1000$ mg/d with/without vertebral fractures	I:95 P:102	In prevalent fracture group, calcium supplementation significantly reduced incident vertebral fracture rate ( $P = 0.023$ )
Bisphosphonates Black et al [55] FIT I 1996	Randomized, placebo controlled	Alendronate 5 mg/d for 2 yr; 10 mg/d thereafter	Women (mean age, 70 yr) with $BMD < 0.68$ g/cm <sup>2</sup> ( $Z < -1.6$ ) with at least one vertebral fracture	I:1022 P:1005	47% reduction in new vertebral fractures ( $P < 0.001$ ) 51% reduction in hip fractures (95% CI 0.23–0.99) 48% reduction in wrist fracture (95% CI 0.31–0.87)
Cummings et al [56] FIT II 1998	Randomized, placebo controlled	Alendronate 5 mg/d for 2 yr; 10 mg/d thereafter	Women (mean age, 67 yr) with $BMD < 0.68$ g/cm <sup>2</sup>	I:2214 P:2218	T score $< -2.5$ : 36% reduction in clinical fractures

			( $Z < -1.6$ ) without vertebral fractures		50% reduction in vertebral fractures T score $> -2.5$ : no significant decrease in risk for fractures
Harris et al [63] VERT-NA 1999	Randomized, placebo controlled	Risedronate 5 mg/d for 3 yr	Ambulatory women (mean age, 69 yr) with two or more vertebral fractures; or one vertebral fracture and low BMD $< 0.83$ g/cm <sup>2</sup> (T $< -2$ )	I:821 P:820	41% reduction in risk of new vertebral fractures ( $P = 0.003$ ) 39% reduction in risk of nonvertebral fractures ( $P = 0.02$ )
Reginster et al [64] VERT-MN 2000	Randomized, placebo controlled	Risedronate 5 mg/d for 3 years	Ambulatory women (mean age, 71 yr) with two or more vertebral fractures; or one vertebral fracture and low BMD $< 0.83$ g/cm <sup>2</sup> (T $< -2$ )	I:408 P:408	49% reduction in risk of new vertebral fractures ( $P < 0.001$ ) 33% reduction in risk of nonvertebral fractures ( $P = 0.06$ )
McClung et al [65] HIP 2001	Randomized, placebo controlled	Risedronate 2.5 mg or 5.0 mg/d for 3 years	I: women 70–79 years of age with osteoporosis (T score $< -2.9$ – $-2.7$ ) II: women $> 80$ years with at least one nonskeletal risk factor for osteoporosis	I:3624 P:1821  I:2573 P:1313	40% reduction in risk of hip fracture ( $P = 0.009$ )  No significant reduction in risk of hip fracture ( $P = 0.35$ )
Calcitonin Chestnut et al [96] PROOF 2000	Randomized, placebo controlled	Nasal calcitonin 100/200/ 400 IU for 5 years	Women (mean age, 68 yr) with one to five vertebral fractures; LS BMD T score $< -2.0$	I:944 P:311	200 IU: 33% – 36% reduction in risk of new vertebral fracture ( $P = 0.03$ ) 100, 400 IU: no significant reduction in risk of new vertebral fracture

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Table 4 (continued)

Author	Study design	Intervention	Population	Sample size	Results
Hormone replacement therapy					
Lindsay et al [78] 1980	Prospective cohort	Mestranol 23.3 µg mean dose	Postoophorectomy patients with preexisting osteoporosis	I:58 P:22	Significant reduction in wedge vertebrae (T4 and L2) in estrogen users
Lufkin et al [77] 1992	Randomized, clinical trial	Transdermal estrogen patch x 3 weeks, with 10 mg/d oral medroxy-progesterone acetate	Women 47–75 years of age with established osteoporosis	I:39 P:39	Significant increase in lumbar spine BMD ( $P = 0.007$ ) No significant difference at hip Lower vertebral fracture risk in estrogen users RR 0.39 (95%CI 0.16–0.95) [based on number of fractures]
Kanis et al [80] MEDOS 1992	Population based case control	—	Women (mean age, 78 yr) who had hip fracture over 1-year period	I:2086 P:3532	Adjusted relative risk for hip fracture 0.55 (95%CI 0.36–0.85; $P = 0.01$ ) in ever users vs never users
Cauley et al [23] 1995	Prospective, cohort	—	Nonblack women >65 yr who were in SOF study	9704	Current estrogen users: Nonspinal fracture — RR 0.69 (95% CI 0.57–0.83) Wrist fracture — RR 0.46 (95% CI 0.29–0.72) Hip fracture — RR 0.80 (95% CI 0.51–1.26) Past estrogen users: No benefit for nonspinal, wrist, or hip fractures

PEPI [72] 1996	Randomized, placebo controlled	Four estrogen + progesterone regimens	Healthy women aged 45–64 yr	I:701 P:174	Active group — mean increases in BMD: spine 3.5%–5%; at hip 1.7% Placebo group — lost BMD at spine –1.8%; at hip –1.7%
Villareal et al [76] 2001	Randomized, placebo controlled	Conjugated estrogen + medroxyprogesterone acetate	Women >75 years of age with physical frailty	I:45 P:22	HRT resulted in significant increase in BMD LS spine — 4.3% vs 0.4% ( <i>P</i> < 0.001) Hip — 1.7% vs –0.1% ( <i>P</i> = 0.02)
Raloxifene Ettinger et al [91] MORE 1999	Randomized, placebo controlled	Raloxifene 60 mg/120 mg/d for 3 years	I: Tscore < -2.5; no vertebral fractures  II: Low BMD + one vertebral fracture or two vertebral fractures	I:3002 P:1522 I:1534  P:770	60 mg/day raloxifene — Vertebral fractures I: 55% decrease (95% CI 0.29–0.71) II: 30% decrease (95% CI 0.56–0.86) Nonvertebral fractures No significant decrease; RR 0.94 (95% CI 0.79–1.12)
Parathyroid hormone Neer et al [102] 2001	Randomized, placebo controlled	20 µg or 40 µg Parathyroid hormone (1-34)	Postmenopausal women (mean age ~ 69 yr) with prior vertebral fractures	I:541 P:544	20 µg I-PTH: 65% decrease in vertebral fracture (95% CI 0.22–0.55) 53% decrease in nonvertebral fractures (95% CI 0.25–0.88)

*Abbreviations:* I, intervention; P, placebo or control; BMD, bone mineral density; RR, relative risk; HRT, hormone replacement therapy.

Table 5  
Medications approved in the United States for osteoporosis

Drugs	Dose
Estradiol, micronized (Estrace)	0.5 mg PO daily
Esterified Estrogens (Estratab, Menast)	0.3 mg PO daily
Estropipate (Ogen)	0.75 mg PO daily
Conjugated equine estrogens (Premarin)	0.625 mg PO daily
Transdermal estradiol (Climara; Estraderm; Vivelle)	6.5 cm <sup>2</sup> patch weekly 10cm <sup>2</sup> patch twice a wk 11cm <sup>2</sup> patch twice a wk
Estrogen Combinations	
Estradiol/norgestimate (Ortho-Prefest)	1 mg daily × 3 days, followed by 1 mg/0.09 mg daily × 3 days, repeated
Estradiol/norethindrone acetate (Activella; Femhert)	1 mg/0.5 mg daily 5 µg/1 mg daily
Conjugated equine estrogen/medroxyprogesterone (Prempro; Premphase)	0.625 mg/2.5 mg PO daily 0.625 mg PO daily days 1–14, then 0.625 mg/5 mg PO daily days 15–28
Alendronate (Fosamax)	10 mg/d or 70 mg/wk (treatment) 5 mg/d or 35 mg/wk (prevention)
Risedronate (Actonel)	5 mg/d
Raloxifene (Evista)	60 mg/d
Calcitonin (Miacalcin nasal spray)	200 IU/d in alternating nostril

WHO BMD criterion for osteoporosis without vertebral fracture (FIT II, T score < -2.5) and in those who have existing vertebral fracture but who do not meet the WHO BMD criterion for osteoporosis (FIT I).

Treatment with alendronate also had significant effects on the physical disability resulting from osteoporotic fractures. In the FIT trial, for women with preexisting vertebral fractures who took alendronate therapy for 3 years, the number of bed-rest days was reduced by 63% (from 5.1 to 1.9 days), and the mean number of limited-activity days was reduced by 16% (from 73.2 to 61.8 days) [58].

*Intermittent dosing.* The efficacy of once weekly versus daily dose of alendronate has been compared in a randomized controlled trial with 889 postmenopausal women (range, 42 to 95 years of age) with osteoporosis [59] with similar increases in lumbar spine BMD in both groups. The incidence of clinical and laboratory adverse effects, including gastrointestinal (GI) intolerance, was also similar although there was a suggestion that serious GI adverse events (ie, perforation, ulcers, and bleeds) might be less in the 70-mg group. Although the study was not powered to show fracture reduction, it can be assumed that the new 70 mg once-weekly dosing regimen is a more convenient and therapeutically equivalent alternative to daily regimen and has been approved by the FDA for treatment of osteoporosis.

*Elderly women.* Elderly women with osteoporosis who participated in a 24-month dose-ranging study with alendronate 1, 2.5, or 5 mg versus placebo [60] were continued on 10 mg of alendronate in an open label extension study [61]. The 12-month extension was conducted to evaluate the safety and confirm the efficacy of 10 mg alendronate in elderly women. A total of 246 women, with ages ranging from 62 to 87 years (68% older than 70 years, 41% older than 75 years, and 12% older than 80 years) enrolled in the open label treatment. The overall number of adverse GI experiences decreased in each group during the extension and only 1% of the subjects withdrew from the study because of an adverse GI effect. They tolerated alendronate therapy well, similar to the younger women, and had significant gains in BMD at lumbar spine and trochanter.

### *Risedronate*

In a randomized, double-blind, placebo-controlled trial [62], risedronate (5 mg/d) increased the lumbar spine BMD from baseline by 4% at 24 months in contrast to no-change in the placebo group ( $P < 0.001$ ) and BMD at femoral neck and trochanter increased by 1% and 3%, respectively, compared with placebo.

The Vertebral Efficacy With Risedronate Therapy study had two arms: North American and multinational (Table 4). In the North American arm [63], risedronate decreased the cumulative new vertebral fracture incidence and non-vertebral fractures by 41% ( $P = 0.003$ ) and 39% ( $P = 0.02$ ), respectively. In the multinational arm, risedronate reduced the risk of new vertebral fractures by 49% ( $P < 0.001$ ) and nonvertebral fractures by 33% ( $P = 0.06$ ) compared with placebo [64].

The Hip Intervention Program (HIP) study enrolled 5445 women (range, 70 to 79 years old) with osteoporosis and 3886 women older than 80 years old with non-skeletal risk factors for osteoporosis (and not low bone mass). All women were randomly assigned to receive treatment with oral risedronate, 2.5 mg or 5 mg, or placebo for 3 years [65]. The BMD at the femoral neck and trochanter was higher in the risedronate group as compared with the placebo group at 6 months and at all time points thereafter. These changes in BMD were similar in both the younger and older group. The incidence of hip fracture in the group of women 70 to 79 years old was 1.9% among those assigned to risedronate and 3.2% among those assigned to placebo (41% reduction,  $P = 0.009$ ). In the group of women 80 years of age and older who were recruited on the basis of clinical risk factors, however, risedronate had no significant reduction in fracture rates. It can be concluded that even at age 80 years, measurement of BMD is important in identifying patients who will benefit from a bisphosphonate.

### *Adverse events*

Bisphosphonates are generally well tolerated. GI side effects may occur, and a small number of patients with erosive esophagitis have been reported with

alendronate [66,67]. Because of this potential problem, patients must take the medication in the morning with a full glass of water (6 to 8 ounces), 30 minutes before first food or drink of the day and remain upright (sitting or standing) for at least 30 minutes after the dose. Esophageal stricture or motility dysfunction is a contraindication to use of bisphosphonates. Numerous endoscopic studies have compared alendronate and risedronate for adverse effects on the esophagus, stomach, and duodenum with conflicting results [66,68]. These are short studies (2 weeks), and it is unknown whether these endoscopic lesions will result in clinically significant outcomes.

### *Duration of use*

It is not yet clear how long bisphosphonate therapy should be given. One major determinant of that answer is what happens when therapy is discontinued. Women receiving alendronate have been followed for 7 years [54]. The lumbar spine BMD continued to show a linear increase in women who continued to receive alendronate over that period. Women who discontinued alendronate at the end of 5 years continued to have stable BMD for up to 2 years after discontinuing alendronate. The bone turnover increased, but not to the elevated values seen in untreated osteoporosis women. The optimal duration of treatment, however, is currently unknown.

### *Prevention studies*

In addition to its efficacy in treating osteoporosis in postmenopausal women, studies have evaluated the use of alendronate for preventing osteoporosis [69–71]. These studies have been done, however, in young postmenopausal women, and no data are available for elderly patients.

### *HRT*

The beneficial effects of hormone replacement on BMD at a variety of skeletal sites have been documented in several randomized, controlled trials in both early and late postmenopausal women [72–75]. In a recent study of older women, estrogen and medroxyprogesterone acetate produced a 1.4% to 3.9% greater difference in BMD at skeletal sites as compared with placebo [76].

One randomized controlled clinical trial showed the effectiveness of HRT in reducing vertebral fractures in women with established osteoporosis; however, the study has been criticized for using number of fractures rather than number of patients with fractures as endpoint [77]. Two other trials have shown vertebral fracture reduction (or a presumed surrogate) in postmenopausal women treated with HRT [78,79]. All these studies were very small, however, and had few elderly subjects.

For hip fractures, the evidence of antifracture efficacy is based primarily on observational data (Table 4). In the Study of Osteoporotic Fractures [23], current estrogen use was associated with a decrease in the risk of wrist fracture (RR = 0.39;

95% CI, 0.24 to 0.64) and for all nonspinal fractures (RR = 0.66; 95% CI, 0.54 to 0.80) when compared with nonestrogen users. The RR for hip fractures was also decreased but not statistically significant. In both the Mediterranean Osteoporosis Study [80] and the Swedish Hip Fracture Study Group [81], current estrogen users were significantly protected against hip fractures, whereas no significant difference was observed for former users.

There are no HRT trials that are both primarily designed and adequately powered to support the observational evidence of fracture risk reduction by HRT. Recently, the presumed skeletal and nonskeletal benefits of HRT have been challenged. The Heart and Estrogen/Progestin Replacement Study—a double-blind, placebo-controlled, randomized trial—was primarily designed to evaluate the effect of HRT on secondary prevention of heart disease, with assessment of fractures being only a secondary endpoint [82]. The authors found no difference between estrogen and placebo users for hip fracture (RR = 1.10; 95% CI, 0.49 to 2.50) or any fracture (RR = 0.95; 95% CI, 0.75 to 1.21). Patients were not enrolled, however, based on low bone mass, and the study was not powered to show fracture reduction. More data on the effect of estrogen on fracture incidence are likely to be available in the coming years as the Women's Health Initiative program in the United States and the Women's International Study of Long Duration Oestrogen after Menopause trial in the United Kingdom are completed.

### *Duration and timing*

An area of concern involves the timing of initiation and duration of HRT. Recent data suggest that women should be started on estrogen within 2 to 7 years of menopause [23,81,83]. In a recent meta-analysis, HRT was found to prevent nonvertebral, hip, and wrist fractures when women commenced treatment before age 60 years; however, there was insufficient evidence that fracture risk was reduced when begun after age 60 [84]. Evidence from other controlled trials showed, however, that estrogen had positive effect on BMD even when started 20 years or more after menopause [77]. Estrogen begun and continued over age 60 years maintained BMD [85], and women older than age 65 years with established osteopenia treated with estrogen [86] had increases in absolute BMD comparable to that observed in younger women. There is growing evidence, however, for an attenuation of the beneficial skeletal effects of HRT after the withdrawal of treatment. This evidence was shown in the Framingham Study [87], in which women treated for 7 years had lost most of the gain in BMD when remeasured 7 years later. Similar findings were also reported from the Swedish Hip Fracture Study [88]. Hence, the duration of therapy necessary to protect women against fragility fractures may well be indefinite.

Compliance with HRT, however, is typically poor because of common side effects and concerns over an increased incidence of breast or endometrial cancer. One major reason to discontinue therapy is irregular uterine bleeding; the amount of which may be less in women on low dose HRT [74]. Thus, low-dose estrogen

in elderly women may prevent bone loss and minimize the side effects seen with higher dose of estrogen.

### *Selective estrogen receptor modulators*

Selective estrogen receptor modulators (SERMs) are compounds that can bind to and activate estrogen receptors but can cause differential estrogenic or antiestrogenic responses in different tissues. Raloxifene was the first SERM approved for osteoporosis.

#### *Raloxifene*

Early studies showed that raloxifene increases lumbar spine and total hip and femur BMD [89,90]. In the Multiple Outcomes of Raloxifene Evaluation study (MORE) [91] (Table 4) for women with low BMD and no prevalent vertebral fracture, the incidence of new vertebral fracture was reduced by 55% (95% CI, 0.29 to 0.71) whereas among the women with prevalent vertebral fractures, the incidence of new vertebral fracture was reduced by 30% (95% CI, 0.56 to 0.86) with use of raloxifene 60 mg/d. The MORE study did not have statistical power to detect a reduction in risk for total nonvertebral fractures or for individual nonvertebral sites. For the pooled raloxifene groups, the RR for total nonvertebral fractures was 0.94 (95% CI, 0.79 to 1.12) as compared with placebo. Similar results were found at the end of 4 years of the trial. Women receiving raloxifene had increased risk of venous thromboembolism ( $\sim 3/1000$ ); a risk similar to estrogen in several series. Hot flashes occur with increased frequency especially in early menopausal women. In contrast to estrogen, raloxifene did not cause vaginal bleeding or breast pain and was associated with a significant lower incidence of breast cancer.

#### *Calcitonin*

Calcitonin is an endogenous hormone secreted by the parafollicular C cells of the thyroid gland, which helps maintain normal calcium homeostasis. Calcitonin acts directly on osteoclasts, with inhibitory effects on bone resorption. In 1994, the FDA approved a new nasal spray preparation formulation of salmon calcitonin.

Previous studies have found calcitonin to be helpful in postmenopausal women with established osteoporosis [92–95]. In a recent 5-year, double-blind, randomized controlled study of intranasal calcitonin on vertebral fracture rate in women with postmenopausal osteoporosis (Prevent Recurrence of Osteoporotic Fractures [PROOF] study) [96] (Table 4), 200 IU salmon calcitonin nasal spray per day significantly reduced the risk of new vertebral fractures by 33% to 36% in women with prevalent vertebral fractures. No significant fracture reduction was seen, however, in those receiving 100 or 400 IU/d. The PROOF study was not powered to detect nonvertebral fracture reduction. A nonsignificant reduction was noted in the risk of nonvertebral fractures in this study compared with placebo. There are two major limitations of the PROOF study, however. First, there was a 59% discontinuation rate for the 5 years of the study, which was higher than

expected. Second, a dose–response curve of nasal calcitonin for fracture reduction was not seen [97]. Adverse effects with intranasal calcitonin are rare. In the PROOF study, a significant increase was noted in only rhinitis [96].

### *Alternative therapies*

Alternative therapies are now being studied for their effect on BMD. Among these are phytoestrogens, which are a diverse group of compounds found in a wide variety of plant foods that are believed to have estrogen-like activity and more recently have been thought to have both estrogenic and antiestrogenic activity [98]. Some preliminary studies had shown a possible role of phytoestrogens in preventing osteoporosis. The Ipriflavone Multicenter European Fracture Study, a prospective, randomized, double-blind, placebo controlled trial (475 postmenopausal women with low BMD), concluded, however, that ipriflavone did not prevent bone loss or affect biochemical markers of bone metabolism [99].

### *Anabolic agents*

In contrast to the current available drugs that slow bone turnover and thereby allow bone formation to exceed bone resorption, anabolic agents, such as PTH, actually stimulate remodeling, preferentially increasing formation over resorption.

Data for effect of PTH on BMD are available from three recent randomized clinical trials [100–102]. In the largest trial, 1637 postmenopausal women were administered 20 or 40  $\mu\text{g}$  human PTH (I-34) or placebo and followed for 21 months [102]. The RR for vertebral fractures in women receiving 20  $\mu\text{g}$  was 0.35 (95% CI, 0.22 to 0.55); for 40  $\mu\text{g}$ , 0.31 (95% CI, 0.19 to 0.50). New nonvertebral fragility fractures occurred in 6% of women in the placebo group and in 3% of those in each PTH group (RR, 0.47 and 0.46, respectively [95% CI, 0.25 to 0.88 and 0.25 to 0.86]). New or worsening back pain was reported by 23% of the women in the placebo group but by only 17% and 16% of those in the 20 and 40  $\mu\text{g}$  PTH groups, respectively ( $P = 0.007$ ). Nausea and headache were the most common side effects, and these occurred infrequently and in a dose-dependent manner. In July 2001, PTH injection (20  $\mu\text{g}$  subcutaneous once a day) received FDA advisory committee approval for postmenopausal osteoporosis.

### *Combination therapy*

Estrogen and bisphosphonates together produce greater gains in BMD than either agent used alone [103,104]. The addition of 10 mg alendronate daily to women receiving estrogen significantly increased spine and hip trochanter BMD over 12 months as compared with estrogen alone [105]. None of these studies are large enough, however, to determine if there is a decrease in the fracture risk with combination therapy.

Combination therapy using anabolic agents (eg, PTH) and antiresorptive agents are being launched. Recent clinical trials of PTH in combination with established estrogen [106,107] have shown a significant increase in both spine

and femoral neck BMD with PTH plus estrogen compared with estrogen alone. Also, the combination decreased vertebral fracture occurrence by 75% to 100%, compared with HRT alone [107]. Thus, PTH and estrogen have a greater effect on bone mass at both spine and femur than either alone.

PTH and bisphosphonates has been evaluated in one open label study after the 1 year, multicenter PTH trial [101]. Women who received either PTH or placebo were given 10 mg alendronate for another year. Women who received alendronate showed a 14.3% increase in spine BMD compared with a 7% increase in those receiving placebo. The response was thus additive. The role of combination therapy in osteoporosis management is not clearly defined at present.

### **Osteoporosis in older men**

Although the incidence of osteoporosis in men is lower than in women, one third of all hip fractures worldwide occur in men. The risk factors for osteoporosis in men age 60 years and older are low femoral neck BMD, quadriceps weakness, low body weight, falls in the preceding year, and a history of fractures in last 5 years [108,121]. The Framingham Osteoporosis Study [24] identified low baseline weight, weight loss, and smoking cigarettes as risk factors for osteoporosis. In a large population-based study of elderly men from the Rancho Bernardo Study [109], low estradiol level was shown to be associated with vertebral fractures, whereas men with low testosterone level consistent with hypogonadism had no significant increased odds for fracture. Although age-related decline in testosterone level has been thought to play a role in decreased bone formation in elderly men, studies involving otherwise healthy older men have been unable to show an association between testosterone levels and bone density [110–114].

Currently, no validated guideline is available for preventing or treating osteoporosis in men; however, there are recent reviews on the management of osteoporosis in men [115,118,122]. Men with history of previous fractures and men with known risk factors for low bone density should be targeted for prevention of osteoporosis and can be offered BMD measurement. The BMD threshold at which therapy should be started is unclear.

Lifestyle modifications, including increasing physical activity, cessation of smoking, and alcohol, should be offered to all men. Calcium and vitamin D supplementation should be recommended for older men even though its evidence for decreasing fractures in older men is limited and conflicting. A large multicenter, randomized controlled trial of alendronate was completed in 241 men with T-score less than 2 at the femoral neck or with osteoporotic fracture [116]. After 2 years, the BMD at lumbar spine increased by 7.1% in those receiving alendronate as compared with 1.8% with placebo ( $P < 0.001$ ), along with significant improvement in BMD at the femoral neck and trochanter. A trend toward fracture reduction was noted in the treated group; however, it did not reach statistical significance.

The use of testosterone therapy in eugonadal men is controversial and present data do not support any benefit associated with routine testosterone replacement in older men [117]. Testosterone replacement is appropriate only in the setting of proven hypogonadism in men with markedly low total testosterone levels. Currently, the role of PTH, growth hormone, and raloxifene are being evaluated for use in men.

## Summary

Osteoporosis is a major clinical problem in older women and men. Almost any bone can fracture as a result of the increased bone fragility of osteoporosis. These fractures are associated with higher health care costs, physical disability, impaired quality of life, and increased mortality. Because the incidence of osteoporotic fracture increases with advancing age, measures to diagnose and prevent osteoporosis and its complications assume a major public health concern. BMD is a valuable tool to identify patients at risk for fracture, to make therapeutic decisions, and to monitor therapy. Several other modifiable and nonmodifiable risk factors for osteoporosis have also been identified.

Treatment of potentially modifiable risk factors along with exercise and calcium and vitamin D supplementation forms an important adjunct to pharmacologic management of osteoporosis. Improved household safety can reduce the risk of falls. Hip protectors have been found to be effective in nursing home population. The pharmacologic options include bisphosphonates, HRT, SERMs and calcitonin. PTH had received FDA advisory committee approval. Alendronate has been approved for treatment of osteoporosis in men, and other treatments for men are under evaluation.

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