Treatment Considerations in the Management of Age-Related Osteoporosis

Craig D. Rubin, M.D.
Associate Professor of Medicine
Geriatrics Section
Division of General Internal Medicine

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Craig D.Rubin MD

Associate Professor Internal Medicine

Dr. Rubin is the past recipient of an academic award from the National Institute on Aging for the study of age-related osteoporosis. Other areas of interest include comprehensive geriatric assessment and the primary care of patients with alzheimer's disease.

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (1). The past few years have brought a growing awareness of the prevalence of this disease. This, in part, has been due to a better understanding of the pathophysiology of osteoporosis, the development of methods to measure bone mass and thereby predicting fracture risk and the introduction of new medications to prevent and treat osteoporosis. This Grand Rounds will review some of these developments with emphasis on involutional osteoporosis and consideration of the older patient.

Over 1 million osteoporotic (fragility) fractures occur in the U.S. annually (2). Most are related to primary or involutional osteoporosis. It is estimated that 250,000 hip fractures occur annually in the U.S. and this number is predicted to double by the year 2040 (3). The median age of hip fracture is 79 years old.

A 50-year-old white woman has a 16% (lifetime risk is similar for a 65 or 80-year-old) chance of sustaining a hip fracture and a 32% risk of suffering a vertebral fracture during her remaining lifetime (4). For comparison, a 50-year-old white woman has a lifetime risk of 22% of having a myocardial infarction, 9% lifetime risk of developing breast cancer and a 3% lifetime risk of developing endometrial cancer (including carcinoma in situ)(5). The lifetime risk of death for 50-year-old white postmenopausal women is 31% for coronary artery disease, 2.8% from hip fractures, 2.8% from breast cancer and 0.7% for endometrial cancer. These figures are helpful to evaluate the risk benefit of screening and treatment recommendations. If estrogen therapy is proven effective in reducing heart disease (the assumption of estrogen replacement therapy [ERT] reduces coronary heart disease is based on observational studies, which may be biased), screening and placing those with low bone density on long-term ERT would be reasonable and comparable with other interventions currently paid for by public and private third party payors (5).

Although hip fracture is the most feared complication of osteoporosis, the consequences of vertebral fractures are also substantial and have been well documented (6,7,8). In addition to the pain and physical disability associated with fractures, other repercussions such as fear of falling and poor self image can lead to functional decline.

Health care expenditures related to osteoporotic fractures in 1995 were estimated at $13.8 billion (9). When adjusted for inflation, the dollar amount is estimated to reach 30-45 billion dollars by the year 2020 (10). These calculations may be overestimated because they generally do not discount for baseline co-morbidity (11), but regardless, the costs are substantial.

Thus, when we consider the aging of our society and the fact that the oldest of the old is growing at the fastest rate, the morbidity, mortality, functional decline and economic consequences from osteoporosis will continue to be a substantial health concern as we enter the new millennium.

Determining Fracture Risk and the Diagnosis of Osteoporosis

In 1994, the World Health Organization (WHO) proposed that the diagnosis of osteoporosis be based on the results of a bone density determination and not solely on the presence of a fracture (12). Briefly, the argument for using a bone density value in making the diagnosis is that bone density is as predictive for future fractures as are other common screening tools in predicting outcomes such as cholesterol level and blood pressure for cardiovascular disease. For every standard deviation (SD) below peak (30-year-old mean) vertebral bone mineral density (BMD), there is an approximate doubling of vertebral fracture risk. For women older than age 65 years, each SD decrease in femoral neck bone mineral density increases the age-adjusted risk for hip fractures by 2.6. In addition, the risk of fracture is progressive so that fracture risk continues to increase regardless of age (in other words, the lower your bone density, the higher your risk of subsequent fracture regardless of age). Therefore, the risk assessment of an individual is determined by their bone density compared to the 30-year-old mean (T score or number of standard deviations from the 30-year-old mean) and not compared to the mean for their age (or Z score). In view of these consideration, the consensus panel assembled by the WHO recommended the diagnostic classification for osteoporosis as a bone density of 2.5 SD below the mean value for premenopausal white women. Those with reduced bone mass and at least one fragility fracture is defined as "established" or severe osteoporosis (see Table 1).

TABLE 1. General Diagnostic Categories in Women*

Normal	BMD or BMC <1 below young adult mean value
Low bone mass (osteopenia)	BMD or BMC >1 but <2.5 SD below young adult mean value
Osteoporosis	BMD or BMC >2.5 SD below young adult mean value
Severe osteoporosis (established osteoporosis)	BMD or BMC >2.5 SD below young adult mean value in the presence of at least one fragility fracture

BMD=Bone Mineral Density
BMC=Bone Mineral Content
SD=Standard Deviation
*WHO Criteria

Using the WHO definitions, about 9.4 million (of which 4.8 million have established osteoporosis), postmenopausal white women have osteoporosis. Another 16.8 million postmenopausal white women have osteopenia defined as a BMD between 1.5 and 2.5 SD below the mean for premenopausal white women (13).

Although bone density is the single most powerful predictor of fracture risk (70-80% of bone strength is attributable to bone mass), other factors independently determine fracture risk and are not considered in the WHO classification of osteoporosis. These include the existence of a prevalent fracture (the presence of fragility fracture increases risk of subsequent fracture as high as five-fold) (14), age (15) (see Fig. 1), other co-morbid conditions, and bone qualities not measured by bone density (16,17).

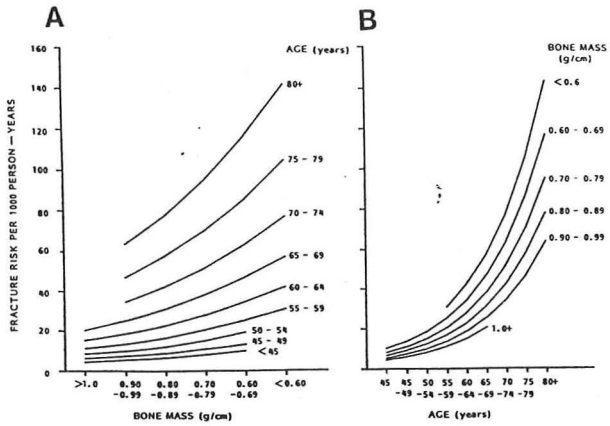


FIG. 1. Estimated incidence of fracture as a function of age and bone mass.

Other criticisms or limitations of the WHO definition is that the cut-off value is relatively arbitrary and will identify some individuals that will never fracture, it is based on the use of single technology and based on values determined in white women. Furthermore, some patients may have fragility fractures but normal or inaccurate bone density measurements due to artifacts such as osteophytes or vascular calcifications, or scoliosis. Patients with prevalent fractures may have normal or high BMD because BMD is an areal measurement, so decreases in area (from a fracture) may result in a higher measurement. In today's health care environment, the WHO definition could result in misuse of guidelines by denying reimbursement for treatment in patients with fragility fractures, but normal bone density measurements.

Although different techniques are available to measure bone mass, each with its own strengths and limitations, dual-energy x-ray absorptiometry (DEXA) is generally the method of choice to measure bone density (18). It is quick, has a low x-ray exposure, and can measure mass at the spine, hip or radius (or other sites) with good precision. These table machines, as they are commonly referred, are large and not portable unless used as a mobile unit. Newer DEXA machines have been developed which use peripheral sites such as the calcaneus or distal radius that are smaller and portable. Also, other technologies such as the use of ultrasound are capable of predicting fracture risk similar to DEXA machines. In addition, quantitative computerized tomography (QCT) or peripheral quantitative computerized tomography (pQCT) yields volumetric measurements and can predict fracture risk. Although the peripheral machines may provide some screening utility, their routine use and role in allowing the physician to diagnose and treat patients is limited. There are a number of reasons for this. First, although measurement of a low bone density at any skeletal site is predictive of fracture risk, the most accurate determination of site specific risk is measurement of the site of interest. For example, measuring the spine would give the most sensitive and specific value for possible spinal fractures. The greater association of hip density with fracture risk compared to other sites is demonstrated by estimating the lifetime risk of hip fracture in 50-year-old women with a radial bone density at the 10th and 90th percentile as 19 and 12 percent, respectively, whereas the same determinations made at the hip would mean a lifetime risk of 25 and 8% (19,20).

In addition, a discordance of measurements is found in some individuals, i.e., the distal radius may be normal but the spine may be low (18). Therefore, obtaining the normal radial value might erroneously diagnose an individual as normal when, in fact, osteoporosis might be present. Secondly, the distribution of low bone density can also be used to assess underlying etiology of bone

loss. That is, a low wrist and hip density, but preserved cancellous sites such as the vertebrae would be illustrative of the pattern of cortical bone loss seen in primary hyperparathyroidism. Third, the ability to monitor the response to a therapeutic intervention generally requires measurement of axial sites, and most therapeutic interventions have little or no effect at sites such as the wrist. So, detecting a change in BMD would be difficult. Lastly, and perhaps most importantly, virtually all recent studies have monitored response to therapy by using table DEXA machines and so other technologies would have little known value in monitoring patients.

Although the relative immobility of the DEXA table scanners may limit their utility in some locations such as rural areas which may not have a machine, their availability is expanding substantially. Currently, peripheral measurements such as the calcaneus or wrist with peripheral DEXA machines or ultrasound technology at best may be useful for screening measures, but a table machine and direct measurement of the spine and/or hip should be performed in order to confirm the peripheral measurement. A table machine is necessary to monitor the effectiveness of therapeutic interventions.

TABLE 2. Clinical Situations in Which Knowledge of the Patient's Bone Mass Could Affect Clinical Management Decisions (Indications for Bone Density Measurements)

- Estrogen deficiency (and would impact treatment decision)
- Suspected osteopenia on plain radiography
- Fragility fracture on plain radiography
- Asymptomatic primary hyperparathyroidism
- Long term use of glucocorticoid
- Management of patients after organ transplantation
- Evaluate the effects of a prescribed intervention on bone mass

The frequency of measurements is also a common question and area of debate. Generally, bone mass measurements should not be taken more frequently than every twelve months. One exception is in patients started on long term steroids where significant bone loss may occur early, a measurement at baseline and six months after initiation is appropriate. Since "experts" cannot agree upon a single site, I suggest the spine as the site of choice as the majority of evidence for fracture reduction from current pharmacologic interventions is based on studies measuring changes in lumbar spine bone mass and/or reduction in vertebral fractures. There is, in fact, very little experimental data showing that pharmacologic interventions prevent hip fractures. Furthermore, only small changes in bone mass occur at the hip. The hip has the advantage of having fewer potential complicating factors in interpreting measurements. That is, in older subjects, osteophytes and vascular calcifications can artificially increase measurements at the spine so some investigators suggest hip BMD is a preferable site for measuring patients over 70 years of age. On the other hand, even in patients with osteophytes and compression fractures the *relative* change in BMD can still be measured. Because most medications result in little or no change at the wrist, measuring or monitoring response to treatment at this site has little utility.

Exceptions occur in specific conditions such as primary hyperparathyroidism where cortical bone density loss is prominent and the measurement at sites with a higher portion of cortical bone is

desirable such as the wrist or femoral neck. In patients with Cushing's disease on chronic steroid therapy, the spine is the primary site of bone loss, so the lumbar spine should be measured.

The precision measurement (precision error) of DEXA is expressed as a percent coefficient of variation (18). This measure indicates the amount of variation in the measurement that is not caused by a biological change in the patient. Ideally 2 separate measurements of the same individual with the same bone mass should yield identical results. However, this is usually not the case. The degree of "noise" or percent coefficient of variation varies depending on the site measured, the machine and the setting where the test is performed. Generally the percent coefficient of variation for DEXA at the lumbar spine and femoral neck is 1.5% to 2.0 % and 2% to 3%, respectively (18). A practical clinical guideline is that the measured change in bone mineral density should be equal to or greater than 2.8 times the coefficient of variation. So a change of 4.2% to 5.6% in the spine and 5.6% to 8.4% at the femoral neck is needed to be considered real.

Risk Factors

The presence of a vertebral fracture (14), advancing age (15), maternal history of hip fracture (21), medications, sedentary lifestyle, small body size (<58 kg) (may be mediated by low hip bone density) (22), co-morbidity and reduced functional status are independent risk factors for fragility fractures (16). However, risk factors are poor predictors of bone mass. Slemenda et al (23) found they could predict spine bone density only 61% of the time. Although bone density is the single most powerful predictor of fracture risk there are factors in addition to bone density which contribute to bone quality other than bone density such as fatigue damage and microarchitectural status which may not be measured by bone densitometers (24). In fact, trabecular bone specimens from younger and older patients with the same apparent density differ in strength with specimens from older patients with 40% lower yield stress (25). Older women matched by areal bone density with younger women have lower frequency of resonance in ulnar cortical bone, consistent with an age-related deterioration in a property of bone independent of areal bone density (26). In addition, non-bony considerations (factors related to falls) are important in assessing a particular individual's risk of fracturing and in developing prevention and treatment strategies. Therefore, when evaluating patients with osteoporosis or osteopenia a wide range of considerations are necessary, similar to the circumstances when evaluating patients with hypertension or hyperlipidemia. Likewise, once a diagnosis of osteoporosis is made, the patient should be evaluated to reverse modifiable factors and exclude "secondary" causes of osteoporosis (see Tables 3 and 4).

TABLE 3. Common Risk Factors for Fractures, Bone Loss, and Falls

Risk Factor	*Modifiable*
Low bone density	Yes
Age	No
History of fragility fractures	No
History of frequent falls	No
Hypogonadism (including postmenopausal women without estrogen)	Yes
Female	No
White	No
Immobility/inactivity	Yes
Biochemical markers of bone turnover	Yes
Bone geometry (longer hip axis length)	No
Alcohol abuse	Yes
Cigarette smoking	Yes
Caffeine excess	Yes
Calcium deficiency	Yes
Vitamin D deficiency	Yes
Poor physical function (muscle weakness, etc.)	Yes
Long-term health problems	Some
Life expectancy (duration of exposure to risk)	No
Genetics (family history)	No
Thyroid hormone excess	Yes
Anticonvulsants	Yes
Long-acting benzodiazepines	Yes
Corticosteroid use	Yes
Estrogen replacement therapy (women)	Yes
Thiazide use	Yes

TABLE 4. Factors Contributing to Osteoporosis

Genetic or constitutional
- White or Asiatic ethnicity
- Family (maternal history of fractures)
- Small body frame
- Long hip axis length
- Premature menopause (<45 years)
- Late menarche

Lifestyle and nutritional
- Nulliparity
- Prolonged secondary amenorrhoea
- Diet low in calcium
- Little exposure to sunlight
- Smoking
- Excessive alcohol intake
- Inactivity
- Prolonged immobilization
- Prolonged parenteral nutrition
- Low body weight

Medical disorders
- Multiple myeloma
- Cushing's syndrome
- Anorexia nervosa
- Malabsorption due to gastrointestinal and hepataobiliary diseases
- Primary hyperparathyroidism
- Thyrotoxicosis
- Primary hypogonadism
- Osteogenesis imperfecta
- Rheumatoid arthritis
- Chronic obstructive lung disease
- Chronic renal failure
- Mastocytosis
- Post-transplantation

Drugs
- Chronic corticosteroid therapy (7.5 mg/day or more of prednisone for more than 6 mos.)
- Excessive thyroid therapy
- Chemotherapy
- Gonadotropin-releasing hormone agonist or antagonist
- Phenytoin and Phenobarbital
- Chronic phosphate-binding antacid use

Physiologic and Clinical Differences Between Type I (Postmenopausal) and Type II (Age-Related) Osteoporosis

Riggs and Melton in 1983 (27,28) proposed the model of Type I and Type II postmenopausal osteoporosis (see Table 5). Type I postmenopausal osteoporosis is characterized by the accelerated phase of bone loss in the early postmenopausal period, affecting primarily cancellous bone and therefore particularly affecting the spine. This rapid phase of bone loss (usually 1-2% per year) lasts generally from 4-8 years and is related to estrogen deficiency. Estrogen appears to control the local production of bone-resorbing cytokines and other factors (29). Reduced estrogen appears to result in increased responsiveness of these paracrine mediators (e.g., interleukin-1) which cause osteoclastic activation and bone resorption. The reduction of estrogen also seems to allow for an increase in bone sensitivity to the bone resorbing effect of PTH. The mobilization of calcium from bone tends to suppress serum PTH levels. Increased loss of urinary calcium and reduced

gastrointestinal calcium absorption maintains normal serum calcium levels (28).

TABLE 5. The Two Types of Involutional Osteoporosis

	Type I	Type II
Age (yr)	51–75	>70
Sex ratio (F:M)	6:1	2:1
Type of bone loss	Mainly trabecular	Trabecular and cortical
Rate of bone loss	Accelerated	Not accelerated
Fracture sites	Vertebrae (crush) and distal radius	Vertebrae (multiple wedge) and hip
Parathyroid function	Decreased	Increased
Calcium absorption	Decreased	Decreased
Metabolism of 25-OH-D to $1,25(OH)_2D$	Secondary decrease	Primary decrease
Main causes	Factors related to menopause	Factors related to aging

The second phase of bone loss occurs 10-20 years after menopause (late menopause) and is associated with a more gradual loss of bone (about 0.5% to 1% per year) and affects cancellous and cortical bone loss in both women and men. This phase has been referred to as Type II osteoporosis (age-related or senile osteoporosis). During this phase of bone loss, a variety of age-related alterations in calcium metabolism results in secondary hyperparathyroidism (30). PTH levels tend to rise (although generally stay within normal range) leading to increased bone turnover. Age-related decline in the renal function, intestinal malabsorption of calcium and altered vitamin D metabolism have all been attributed to the rise in PTH. In addition, senescent changes in osteoblast function cause reduced bone formation (31,32).

It has always been acknowledged that this model is an oversimplification and that overlap exists. Both acute estrogen deficiency and changes associated with aging are occurring at the same time. Recently, Riggs et al. have modified their original postulate and have suggested that the etiology of both the early and late bone loss in women and bone loss in men are related to estrogen deficiency (33). In their model they propose that early bone loss occurs in much the same way as their original model, but the bone loss in the late menopausal period and in men is also related to estrogen. Whereas the rapid bone loss in early menopause is related to direct skeletal consequences of reduced estrogen levels, the later physiologic changes can be explained by extraskeletal effects of reduced estrogen. These changes cause the secondary hyperparathyroidism which has been implicated in the slow and progressive age-related bone loss. The extraskeletal effects occur in the gastrointestinal tract, kidneys and possibly the parathyroid gland. In addition, they speculate that estrogen deficiency may directly cause decreased osteoblastic function but evidence for this at the present time is lacking. The contribution of estrogen deficiency as well as declining osteoblastic function was recognized by Fuller Albright six decades ago (45A). It remains likely that osteoblastic function has a critical role in the age-related decline in bone mass. Whether it is directly related to estrogen is still an area that needs further investigation.

The role of estrogen deficiency in the pathogenesis of secondary hyperparathyroidism is suggested by a variety of studies that found that estrogen reverses many of changes of age-related physiology in the intestine, kidney and parathyroid gland (34-36).

Why skeletal effects of estrogen predominate early and extra skeletal effects predominate later is not clear (37). In addition, as the authors acknowledge, the model also doesn't clarify why PTH levels

should be low early but then progressively rise. There may certainly be other factors independent of estrogen that account for increased PTH such as age-related change in kidney function, reduced dietary intake of calcium and/or vitamin D, intestinal malabsorption of calcium from vitamin D resistance (31) and/or vitamin D independent mechanisms of calcium malabsorption (30,38).

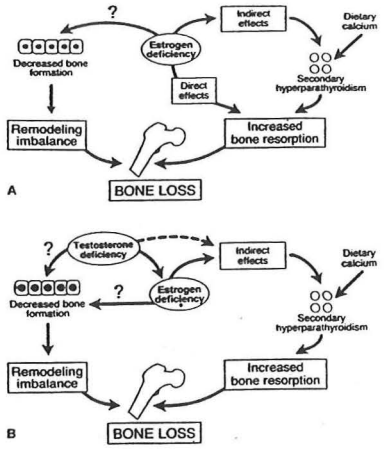


FIG. 2. Schematic representative of unitary model for bone loss in postmenopausal women (A) and in aging men (B).

It is known that men as well as women lose bone later in life and that after menopause, the reduction in both sexes shows a similar rate of decline. The estrogen deficiency model could also explain bone loss in aging men. First, bone loss in aging men seem to correlate better with estrogen levels than with declining androgen levels (39,40). Second, there have been a number of reports of men with a variety of estrogen related deficiencies that result in osteoporosis. Smith and colleagues (41) reported a 28-year-old man with normal serum testosterone, elevated serum estradiol, estrone, FSH, LH, and a lumbar T-score of -3.1 and increased biochemical markers of bone turnover. The patient was found to have a mutation in the estrogen-receptor gene. Administration of estrogen resulted in no change in bone mass nor did it suppress markers of bone turnover (although serum estrogen levels increased 10 fold). Morishima et al. (42) investigated siblings with aromatase deficiency (aromatase catalyzes the conversion of androgens to estrogens) and found the male sibling to be of normal stature but was osteoporotic and had elevated serum androgens but reduced serum estrogens. Carani et al. found that estrogen administration but not androgen increased bone mineral density in an osteoporotic male with aromatase deficiency (43). Morishima et al. in a separate report found a similar response to estrogen in their patient (44).

Another factor contributing to age-related bone loss may be due to the interaction of muscle mass and function and bone density. While discussing the pathophysiology of osteoporosis in 1947, Albright writes:

> "It follows that an osteoblast will stop producing if the skeleton is put at rest by being immobilized in a plaster cast or by virtue of paralysis of muscles pulling on the

skeleton. This aspect of the subject is so self-evident that it is only mentioned here for completeness sake. ...Disuse atrophy is also a factor in the osteoporosis of old age" (45).

Frost points out that most paradigms for the slow bone loss associated with aging humans invoke nonmechanical factors (46,47). He proposes a biomechanical explanation to add to the current hormonal and dietary influences of bone loss. As we grow, much of skeletal response is adaptive to the loads applied to the skeleton. Most of this response is by bone modeling which occurs as an uncoupled phenomena with bone being laid down on the periosteal surface and resorbed on the endosteal side. Once peak skeletal mass is achieved, the skeleton continues to undergo constant remodeling which is the coupled bone resorbing:formation process that characterizes much of bone physiology later in life. It is also the repair mechanism for fatigue damage. As we age, it has been proposed that the accompanying reduction in skeletal mass is related to age-related reductions in muscle mass and activity. Reduced skeletal loading leads to bone loss by activating bone remodeling.

This model could explain the finding that inactivity leads to substantial reduction in bone mass (turning off bone modeling and turning on bone remodeling) and physical activity in adult life seems to maintain bone mass but has modest effect at increasing bone mass (activity or exercise reduces remodeling but modeling is not stimulated beyond genetically determined parameters).

Management Considerations

TABLE 6. Clinical Evaluation

Routine
History and physical examination
Blood cell count, sedimentation rate, serum calcium, albumin, phosphate, alkaline phosphatase, liver transaminases, serum protein electrophoresis, urinalysis
Radiograph of lumbar and thoracic spinal column
Bone mass measurement
Testosterone and gonadotrophins (in men)
Optional
24-hour urinary calcium
Serum and urine markers of bone turnover
Serum PTH, 25-OHD, TSH
Gonadotrophins
Urinary free cortisol

How to treat and manage patients with osteopenia or osteoporosis depends on the individual patient and their clinical circumstances. The issues surrounding perimenopausal women are often very different from the 80 year old. Before going on to prescribing a medication, all patients should receive a careful evaluation to identify secondary causes of osteoporosis (see Table 6). Although much has been written and is hoped for the role of biochemical markers of bone turnover in the diagnosis and management of osteoporosis, their routine use is not indicated at this point in time. Diet, exercise and fall prevention counseling is part of the management of patients with osteoporosis and should not be overlooked.

For patients started on medications, BMD should be monitored as mentioned above to measure the impact of the intervention. One would not consider beginning a patient on an antihypertensive medication without checking the blood pressure response.

Over the past few years there have been a growing number of agents available for the prevention (prevent bone loss) and treatment (increase bone mass and prevent fractures in high risk patients) of osteoporosis. The following is a summary of the currently available agents for consideration.

Estrogen

The antiresorptive effect of estrogen is well established and prevents bone loss at all sites (48). Unfortunately, the evidence that estrogen reduces fractures comes from observational studies (49-62).

There is scant data from long-term randomized controlled trials regarding the efficacy of estrogen in the treatment of osteoporosis (56). In general, the existing information regarding the efficacy of estrogen in preventing fractures can be summarized as follows: estrogen appears to prevent fractures with the best evidence suggesting therapy should be started early after menopause and then continued indefinitely. The greatest fracture reduction seems to occur between the age of 50 to 70 years with less certainty of its efficacy after age 70 (48,49,53,57). Unfortunately there are few studies which have included older individuals and it is at age 80 and older that the greatest incidence of fractures occur. The seemingly reduced efficacy of fracture reduction (both spinal and hip) may be because other factors (i.e., falls) overwhelm issues of bone strength (63). It should be emphasized that in the absence of clinical studies, it cannot be concluded that estrogen is not effective in reducing fractures late in life and even if started for the first time at an advanced age. Since outcome events (fractures) occur at the highest rate in later years it is possible that estrogen started after 75 years of age may be more effective in reducing fractures than if started earlier. It is hoped that results from the Women's Health Initiative Studies, which should be available in about six years will help in guiding recommendations for use in older patients.

There have been some recently published studies that have contributed to our knowledge in prescribing estrogen therapy. The Postmenopausal Estrogen/Progestin Interventions (PEPI) (64) trial has shown that conjugated estrogen given continuously with a progestin is as effective in preventing bone loss than if the progestin is given intermittently. (For women with an intact uterus, use of a progestational agent is necessary to reduce the risk of uterine cancer)(see Figs. 3 and 4).

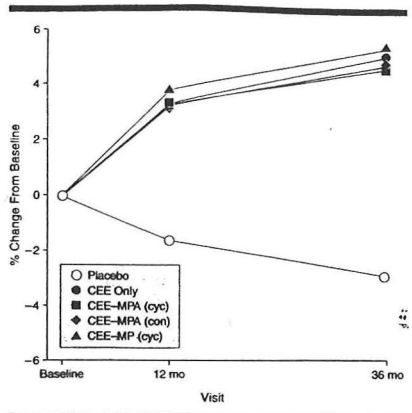


Figure 3 —Unadjusted mean percent change in bone mineral density in the spine by treatment assignment and visit: adherent PEPI participants only. See Table 1 footnotes for explanation of treatment groups and definitions.

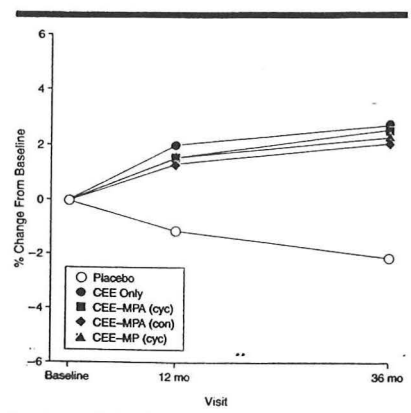
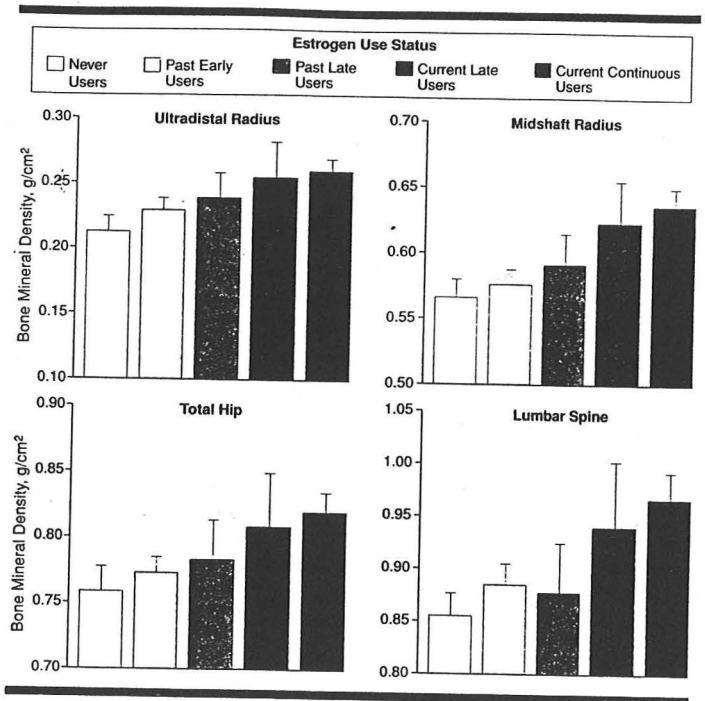


Figure 4 —Unadjusted mean percent change in bone mineral density in the hip by treatment assignment and visit: adherent PEPI participants only. See Table 1 footnotes for explanation of the treatment groups and definitions.

(Source: JAMA 1996; 276:1394)

Results from the Rancho Bernardo Study (65), a cross-sectional study of 740 women ages 60 to 98 years found that estrogen started in the menopausal period and used continuously had the highest bone density. In addition, current users which began estrogen after 60 years of age had nearly as high of BMD as those starting earlier. Caution, however, should be exercised in not over-interpreting these results since only 29 subjects of the 740 participants started estrogen after 60 years of age. This was an ambulatory group of normal white women and not necessarily with reduced bone mass. There were no fracture outcomes reported (see Fig. 5).



Mean bone mineral density (gm/cm²) (95% confidence interval) by estrogen use groups adjusted for age, body mass index, total calcium intake, bilateral oophorectomy, current smoking, alcohol use, exercise, and current use of thiazide diuretics, thyroid hormone, and oral corticosteroids.

FIG. 5 *(Source: JAMA 1997; 277:545)*

The one randomized controlled trial to assess estrogen's efficacy in reducing fractures found that using 17β estradiol increased bone mineral density at the spine (5%) and trochanter (7.6%) but not femoral neck (but maintained it), reduced vertebral fractures, and reduced markers of bone turnover (66). Eight fractures occurred in 7 of 34 women (21%) given HRT, and 20 fractures occurred in 12 of 34 women (35%) given placebo. The reduction in numbers of patients with fractures was not statistically significant. The subjects' ages ranged from 47 to 75 years (median 65 years) and all had established osteoporosis. The short duration of the study (1 year) limits interpretation of their findings. A letter to the editor was published regarding a 3-year follow-up period of 29 of the 39 subjects in the estrogen group and cross over of some of the 39 subjects in the control group (67). Bone mineral density reached an asymptote between the second and third years with an overall increase of 12% over baseline. No information was reported regarding fractures at year 3.

A major concern regarding estrogen use is the low patient compliance. For some patients, a bone density determination may assist in deciding on therapy (68). The lowest effective dose of conjugated estrogen (or its equivalent) that preserves bone density is 0.625 mg daily. Transdermal estrogen (estradiol) preparations also effectively inhibit postmenopausal bone loss (50). A recently published study in normal early postmenopausal women (within 4 years of menopause) supplemented with 1000mg/d of calcium citrate or calcium carbonate found 0.3 mg/d of esterified estrogen maintained bone density at the spine and hip. The 0.3 mg dose increased BMD 1.76% versus placebo and the 0.625 dose increased BMD 2.8% (69).

The ongoing concern regarding the risk of breast cancer (whether justified or not) will cloud the decision to take estrogen for some patients (70,71). Lastly, the potential cardiovascular benefits, especially for those with coronary heart disease, is another consideration in patients selecting patients for estrogen replacement therapy (5).

Calcium

Adequate calcium and vitamin D intake is critical for bone health. The actual postmenopausal bone mass attained is in part dependent on genetics, physical activity and nutrition. For these reasons, the former U.S. Surgeon General, C. Everret Koop, described osteoporosis as a pediatric disease (72).

Calcium supplementation is important in maintaining bone density during menopause, but, by itself, does not appear as effective as estrogen during the early (first 5 years) (73) postmenopausal period. Calcium supplementation can eliminate bone loss in osteoporotic patients and healthy older patients. (74-80). The lack of efficacy in blocking bone resorption noted in some trials may be related to dose and bioavailability of the form used (79,81). The provision of modest doses of calcium and vitamin D to elderly nursing home patients with marginal intake of these nutrients has resulted in an abrupt decrease in fractures (82). In ambulatory older subjects (over 65 years), calcium and vitamin D supplementation has also decreased fractures (74,80) (see Fig. 6).

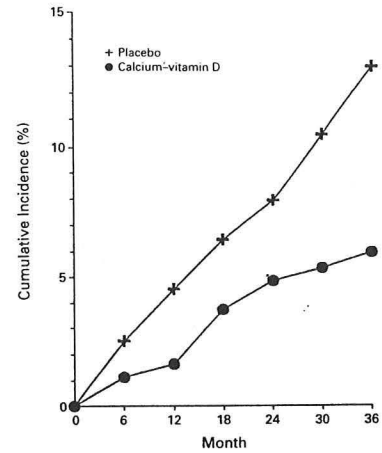


FIG. 6. Cumulative percentage of all 389 subjects with a first nonvertebral fracture, according to study group. By 36 mos, 26 of 202 subjects in the placebo group and 11 of 187 subjects in the calcium-vitamin D group had had a fracture (P=0.02). *(Source: N. Eng. J. Med., Sept. 4, 1997, pg. 674)*

McKane, et al. (83) studied elderly women who were maintained for 3 years on usual calcium intake (815 mg) or high intake calcium (2414 mg) group and a reference group of normal young adult women whose calcium intake was similar to the usual calcium intake group. Parathyroid gland secretory capacity was assessed during induced hypocalcemia and it was determined that the high calcium group and the young reference group demonstrated similar parathyroid secretory capacity as well as similar changes in biochemical markers of bone turnover. The usual elderly calcium group had increased bone turnover, higher levels of serum PTH. Their findings suggest that age-related increases in calcium requirements can be reversed with adequate calcium supplementation. In a 4 year randomized trial reported by Riggs et al., supplementing older ambulatory women (mean age 66, range 61 to 70 years) without osteoporotic fractures with calcium citrate (1600mg/d) versus placebo found that BMD at the lumbar spine and proximal femur were maintained (increased 1-2 % from baseline) (84). Serum PTH and urinary free pyridinoline were reduced suggesting age-related increases in bone turnover were reduced with calcium supplementation.

The beneficial effect of calcium seems primarily related to the reduction of PTH mediated bone resorption and decreased bone turnover. The adequate provision of calcium is important when administering other bone active agents and should not be overlooked. In patients with malabsorption syndromes, this is particularly critical since administration of potent antiresorptive agents may block the only mechanism (bone stores) to maintain circulating calcium levels and can precipitate profound hypocalcemia and tetany.

Women over the age of 65 years should consume at least 1500 mg of calcium a day (85). Men over 65 years should also consume 1500 mg of calcium daily. In the elderly, we favor calcium citrate because of its greater bioavailability and apparent effectiveness in maintaining bone mass at axial and appendicular skeletal sites (70,81). Men and women over 65 years should consume 600-800 I.U. of vitamin D daily (86,87).

Bisphosphonates

The bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption (88). They are analogues of pyrophosphate but are resistant to enzymatic hydrolysis. Alendronate is currently the only bisphosphonate which has received FDA approval for the treatment and prevention of osteoporosis. A growing number of bisphosphonates (etidronate, pamidronate, tiludronate and residronate, and others) are under investigation and/or are available for other indications (Paget's disease of bone and hypercalcemia of malignancy). Since 1995 when alendronate first became available, there have been a number of studies published documenting its effectiveness in preventing bone loss in the early postmenopausal period and increasing bone mass and reducing fracture risk in patients with osteoporosis (89-98).

In the multinational, multicentered study by Liberman et al. (89), osteoporotic (T score > 2.5) patients (20% with baseline vertebral fractures) with a mean age of 64 years were randomized to a variety of doses. At the 10 mg/d dose, BMD at the lumbar spine increased 8.8% at 36 months compared to placebo and 5.9 % in the femoral neck (P<0.001). The increases in BMD in the spine were similar regardless of bone turnover or age. The combined groups (U.S. and multinational had a reduction in vertebral fractures by 48%, 22 of 355 in the placebo and 17 of 526 in treatment groups, 6.2% vs. 3.2% respectively).

The Fracture Intervention Trial (90) (see Table 7) studied the effect of alendronate in osteoporotic (all with baseline femoral neck BMD with a T score of <2.1) women between 55-81 years of age with and without vertebral fractures. Black et al. reported the findings from the 2027 subjects randomized in the fracture arm of the study. BMD increased 4% at the femoral neck and 6.2 % at the lumbar spine at 36 months. The risk of a new vertebral fracture was 47% lower in the alendronate group compared to placebo. Although there were few hip fractures, the treatment group had a 50% reduction in hip fractures, 2.2%. vs. 1.1% (22 vs. 11 events) or a 1% reduction in absolute risk. A subgroup analysis found the reduction in vertebral fractures was similar for those less than or greater than 75 years old, in those with 1 or greater than 2 baseline fractures and in those with hip BMD < or > .59 mg/cm^2 (93). In the 4,432 women in the non-fracture group of the FIT trial, a preliminary report after a mean treatment period of 4.25 years found the BMD in treatment group increased spine BMD by 6.8% and vertebral fractures decreased by 51% or 3.5% in placebo group vs 1.7% in the alendronate group (97).

TABLE 7.

	Women with at least one fracture		Relative hazard (95% CI)
	Placebo	Alendronate	
Any clinical fracture*	183 (18·2%)	139 (13·6%)	0·72 (0·58–0·90)
Type of fracture			
Any non-vertebral	148 (14·7%)	122 (11·9%)	0·80 (0·63–1·01)
Hip	22 (2·2%)	11 (1·1%)	0·49 (0·23–0·99)
Wrist	41 (4·1%)	22 (2·2%)	0·52 (0·31–0·87)
Other†	99 (9·9%)	100 (9·8%)	0·99 (0·75–1·31)

*Including clinical vertebral fracture.

†Placebo *vs* alendronate: shoulder 3 *vs* 2, arm 22 *vs* 21, hand 7*vs* 5, fingers 6 *vs* 7, other small wrist bones 0 *vs* 3, ribs 12 *vs* 15, chest/sternum 1 *vs* 3, pelvis 9 *vs* 6, coccyx/sacrum 0 *vs* 2, leg 12 *vs* 9, ankle 10 *vs* 15, foot/metatarsal 17 *vs* 14, toes 9 *vs* 10, peri-prosthetic 1 *vs* 0.

(Source: Lancet Vol. 348, Dec. 7, 1996)

In the Early Postmenopausal Intervention Cohort Study Group (EPIC), the ability of alendronate to prevent bone loss in women under 60 years of age was assessed (95). At a dose of 5 mg alendronate prevented bone loss at the lumbar spine and hip (but not distal forearm) compared to placebo. Estrogen-progestin therapy was more effective than alendronate at all sites. The BMD increase occurred mostly in the first year, rising by 2.7% and by 0.8% in the second year. The increase in the second year, although small, was statistically significant. Five year data from a study in early postmenopausal women found alendronate increased BMD 2.9 % over 5 years. As in all antiresorptive and bisphosphonate trials, the majority of increase occurred in the first 6 months to 1 year. There was no continuous increase in bone mass in this trial but density was preserved compared to placebo at both the spine and hip (97). There was bone loss at the wrist in the alendronate group but was attenuated compared to the placebo group.

Because of the long duration of action of bisphosphonates there is interest in treating patients on an intermittent basis. Giving alendronate at a higher dose but perhaps on a weekly basis is being studied. This dosing format may decrease the incidence of G.I. intolerance. Stock et al. reported the result of stopping alendronate after 2 years of therapy and found in patients receiving 10 mg a day that biochemical markers of bone turnover remained low a year after discontinuing therapy and BMD at the spine and hip were maintained (92) (see Fig. 6).

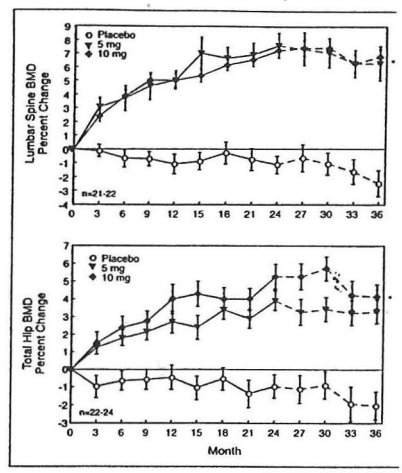


Fig. 6. *(Source: Am. J. Med. 103:293)*

An important consideration in the use of bisphosphonates are their relative selectivity at a given dose for inhibiting bone resorption versus mineralization. If an agent inhibits both bone resorption and mineralization at the same dose, osteomalacic bone could result. The dose at which alendronate inhibits mineralization relative to its ability to inhibit bone resorption is reported to be 1000 to 1 (88). For this reason, alendronate can be given on a daily basis and at least three year experience has found no evidence of mineralization defects or osteomalacia (100).

Because less than 1% (0.78%) of drug is absorbed, it is critical that compliance to treatment recommendations are closely followed in order to maximize effectiveness and minimize side-effects (upper G.I. intolerance, ulcers). Alendronate should be taken with 6 to 8 oz. of **plain water** on an empty stomach at least 30 minutes before breakfast (study patients were instructed to wait 60 minutes). The medication should not be taken with juice or coffee or anything other than water because of the risk of eliminating absorption of the drug. Patients should remain standing or sitting (should not recline) to avoid impairing esophageal transit and diminish the chance of producing esophageal erosions (101-103).

Nasal Salmon Calcitonin

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland. It inhibits osteoclastic activity thereby preventing bone resorption (104). Salmon calcitonin has an advantage to mammalian hormone because of greater potency and longer duration of action. The parenteral form of calcitonin has been approved by the FDA for the treatment of postmenopausal osteoporosis. However, its mode of administration, cost, and side-effects (particularly flushing, nausea and vomiting), has limited its use. In 1995, the FDA approved a nasal spray formulation of salmon calcitonin easing administration and avoiding many of the side-effects associated with parenteral usage. Indication for use is for women with postmenopausal osteoporosis who are greater than five years' post-menopause.

Nasal calcitonin has been studied in multiple clinical trials (105-112). It has a modest affect in maintaining bone mass in the spine with no effect in maintaining hip or forearm bone mass.

There is currently very little evidence that nasal calcitonin reduces fracture risk (107). In the only study to show an antifracture effect, there were 7 fractures in the placebo group and 5 in the calcitonin with one method of fracture determination and 6 in the placebo and 4 in the calcitonin group by using a different method. There were multiple doses (placebo, 50, 100, 200) and pooling of the data was not preplanned. There was no difference in peripheral fractures between groups. The Prevent Recurrence of Osteoporotic Fractures (PROOF) is a 5 year multicenter trial of 1175 women from 42 U.S. centers with at least one vertebral fracture at baseline and a BMD of < 2 SD (T score of 2 or less) which is comparing nasal salmon calcitonin at three different doses vs placebo (113). A three year interim analysis found that there was no significant difference in BMD compared to placebo (lumbar density mean change from baseline was 1.06 %, 1.35%, 1.26%, and 1.51 % for placebo, 100, 200, 400 IU treatment groups, respectively. The reduction in RR of new vertebral fractures compared to placebo group was 37% for the 200 IU group. There were 33 patients (12%) with at least one new vertebral fracture in the 200 IU group and 50 (19.8%) with at least one new vertebral fracture in the placebo group ($p<0.037$). More than 600 patients are continuing in the study (nearly 50% drop out). These preliminary findings suggest that nasal calcitonin may reduce the risk of vertebral compression fractures in patients with established osteoporosis. The mechanism of fracture reduction is unclear given the lack of impact on bone density.

Calcitonin has been reported to have central opioid properties and may be helpful in reducing pain from acute osteoporotic fractures (114). However, the clinical efficacy of calcitonin as an analgesic is uncertain. In patients with acute fractures, some experts suggest trying therapy for a week and

stopping if no clear response to pain is noted. Intranasal calcitonin appears to be well tolerated and few patients have complained of nasal irritation and congestion. Baseline and periodic nasal examinations should be performed. The recommended dose is 200 I.U. per day administered intra nasally, alternating nostrils daily.

SERM

The estrogen receptor contains two distinct domains which are required for transcriptional activation (AF-1 and AF-2) of the gene. Selective estrogen receptor modulators (SERM) are drugs with tissue-selective estrogen effects. The differential activation of the domains is responsible for the tissue selectivity exhibited by these agents (115,116). The ideal SERM would have an estrogen agonist response in bone and the cardiovascular system and an estrogen antagonist response in breast tissue and the uterus. Raloxifene is the first SERM approved for the prevention of osteoporosis. It is a non-steroidal benzothiophene which appears to have at least some agonist properties in bone, the cardiovascular system and is antagonistic or neutral in the breast and uterus (Fig. 7).

Delmas et al. (115) reported the interim findings of a European trial comparing placebo (400-600 mg of elemental calcium) to varying doses of raloxifene in 601 early postmenopausal women. Subjects had lumbar T-scores of -2.5 to 2.0 (almost 55% with osteopenia but patients with osteoporosis were excluded). In patients taking raloxifene markers of bone turnover decreased, BMD increased (see Fig. 8) modestly at trabecular and cancellous sites, total and LDL cholesterol were reduced, and there was no evidence of endometrial hypertrophy as assessed by transvaginal ultrasound. HDL and triglyceride levels remained unchanged and hot flashes occurred in both groups in similar numbers.

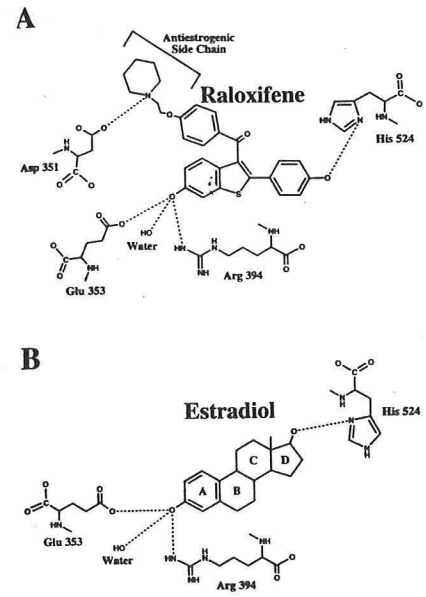


FIG. 7. *(Source: Cancer Research 1998; 58:1873).*

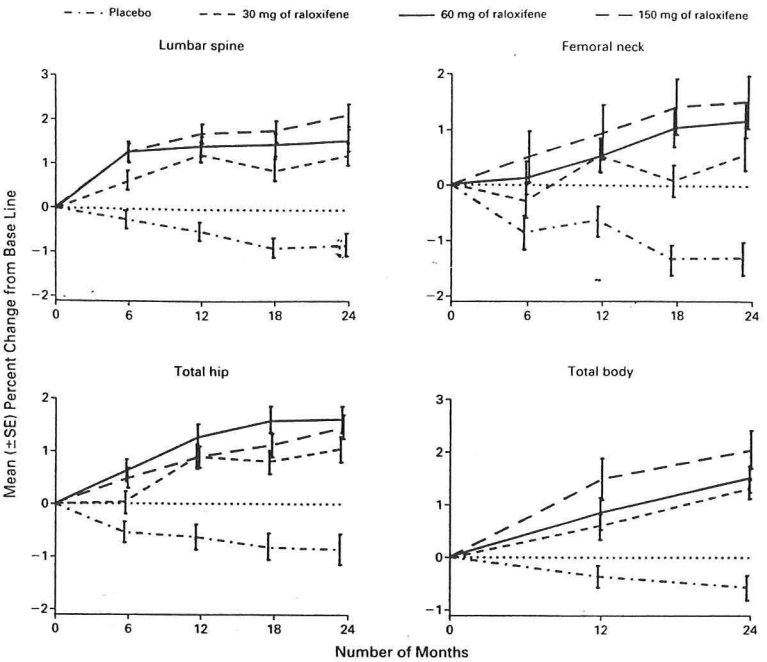


FIG. 8. Mean percent change in bone mineral density in postmenopausal women given Raloxifene or Placebo for two years. *(Source: N. Eng. J. Med., Dec. 4, 1997, pg. 1644).*

For the group receiving 60 mg\day of raloxifene compared to placebo, the difference in BMD at 24 months at the lumbar spine was 2.4%, 2.4 % for the total hip and 2.5% for the femoral neck ($p<0.03$). The increase compared to baseline was 1.6%, 1.6%, 1.2% for the spine, total hip and femoral neck respectively. There was no difference in the drop out rate between groups (25%). Unfortunately it is unclear why the placebo group received a substandard dose of calcium (Tables 8 and 9).

TABLE 8.

MEAN PERCENT CHANGES FROM BASE LINE IN BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN GIVEN RALOXIFENE OR PLACEBO FOR TWO YEARS.*

SITE	PLACEBO	RALOXIFENE†		
		30 mg	60 mg	150 mg
Lumbar spine	−0.8±0.3	1.3±0.3	1.6±0.3	2.2±0.3
Hip	−0.8±0.3	1.0±0.2	1.6±0.2	1.5±0.2
Femoral neck	−1.3±0.3	0.6±0.3	1.2±0.3	1.5±0.5
Total body	−0.6±0.2	1.2±0.2	1.4±0.2	1.9±0.4

*Plus–minus values are means ±SE.

†All values are significantly different from those for placebo ($P<0.03$).

TABLE 9.

MEDIAN PERCENT CHANGES FROM BASE LINE IN SERUM LIPID CONCENTRATIONS IN POSTMENOPAUSAL WOMEN GIVEN RALOXIFENE OR PLACEBO FOR TWO YEARS.*

SERUM LIPID	PLACEBO	RALOXIFENE		
		30 mg	60 mg	150 mg
Cholesterol				
Total	−1.2±0.8	−5.2±1.2†	−6.4±1.1†	−9.7±1.8†
LDL	−1.0±1.5	−6.2±0.8†	−10.1±1.4†	−14.1±1.6†
HDL	−4.7±1.0	−3.1±1.5	−3.7±0.8	−4.5±0.9
Triglycerides	0.0±2.1	0.0±5.5	3.2±3.1	0.5±4.1

*Plus–minus values are medians ±SE. Standard errors were estimated by the d-delete jackknife method.

†Value is significantly different from that for placebo ($P<0.05$).

An unpublished pharmaceutical report comparing placebo, raloxifene and HRT found that total hip BMD at 24 months increased 2%, 0.5% in the estrogen and raloxifene group and decreased about 0.5 % in the placebo group. There are large on going trials to examine whether raloxifene decreases fracture rate.

In all placebo-controlled trials of raloxifene involving approximately 10,400 women, the RR of DVT and pulmonary embolism combined was 3.0, which is similar to the rate reported for estrogen (117). According to the package insert raloxifine should be discontinued at least 72 hours prior to and during prolonged immobilization and resumed only after the patient is fully ambulatory.

An abstract reported at the annual meeting of the American Society of Clinical Oncology, raloxifine reduced the risk of developing breast cancer by 70%. In a study of 7,705 postmenopausal women with osteoporosis, 0.21% of women taking raloxifene (either 60 or 120 mg) developed breast cancer during a 30-month period compared with 0.82% in the placebo group. Patients in the study overall had a lower rate of breast cancer than the general population and were not high risk patients as in the tamoxifen study.

Therefore, raloxifene is an antiresorptive agent and appears to be an effective alternative to estrogen and alendronate in the prevention of bone loss in the early postmenopausal period. The decision to use it will depend on the patients profile. It is not indicated for the treatment of osteoporosis at the present time but large scale studies are currently in progress.

Closing Remarks:

A great deal of progress has been made in our understanding of the pathophysiology, prevention and treatment of osteoporosis over the past 10 years. A common response not long ago from physicians and patients alike regarding the treatment of osteoporosis was that "there is nothing that can be done". This sentiment is now clearly outdated. The evaluation of patients require the synthesis of a diverse set of individual patient characteristics. Specific selection of therapy will vary depending on these characteristics, not unlike the approach to the management of the hypertensive patient.

Much work needs to be done to further our understanding of the pathophysiology, screening and treatment of osteoporosis. The prevention of hip fractures in particular is challenging and will require multifaceted approach. The refinement of how best to use current therapies and the development of newer ones including bone stimulating agents (fluoride, PTH, growth factors) will bring further advances to our treatment armamentarium in the near future. And finally I close by quoting the remarks offered by Fuller Albright in 1947 (47) in concluding a lecture on osteoporosis:

1. I have told you more about osteoporosis than I know.
2. What I have told you is subject to change without notice
3. I hope I have raised more questions than I have given answers.
4. In any case, as usual, a lot more work is necessary.

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