Importance of Early Diagnosis and Treatment of Osteoporosis to Prevent Fractures

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Abstract

Osteoporosis affects about 10 million individuals in the United States, a number that is expected to increase substantially in coming decades as the elderly population burgeons. The chief debilitating consequence of osteoporosis, fracture, will affect about half the women and a third of the men in their lifetime, posing a daunting challenge to managed healthcare systems in terms of delivering optimal care and restraining cost. By encouraging optimal postfracture follow-up care and identifying those members at higher risk for fracture and in need of prompt treatment, managed care organizations can enhance the cost-effective management of osteoporosis, dampening downstream costs. This manuscript reviews the pathophysiology of osteoporosis, examines issues related to the diagnosis of osteoporosis, especially the role of bone mineral density measurement, and focuses on the impact of various treatment options in reducing fracture risk. Early assessment and treatment emerge as medically prudent steps in reducing the risk for osteoporosis-related fracture.

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A major and growing public health concern, osteoporosis substantially increases the risk for fracture, and, in turn, early disability and mortality. The National Osteoporosis Foundation estimates that, in the United States, 10 million individuals, 80% of whom are women, already have osteoporosis, with an additional 34 million individuals at risk because of low bone mass.[1] The prevalence of low bone density increases dramatically with age, affecting 37% of women between the ages of 50 and 59 years, 50% between the ages of 60 and 69 years, 75% between 70 and 79 years, and 87% of women over age 80.[2] In 2001, 27% of women and 5% of men receiving Medicare had been diagnosed with osteoporosis.[3]

Osteoporosis is responsible for more than 1.5 million fractures annually—700 000 vertebral and 850 000 nonvertebral, including 300 000 hip fractures.[4] In their lifetime, 30% to 50% of women and 15% to 30% of men will incur an osteoporosis-related fracture.[5] For healthcare systems, osteoporosis-related fractures will become an increasingly important driver of healthcare costs over the coming decades. Currently, the annual estimated direct cost for the treatment of osteoporotic fracture ($10 billion-$18 billion) is at least comparable with Medicare expenditures for coronary heart disease ($10.6 billion).[1,6,7] By 2020, healthcare spending for osteoporosis-related fractures is anticipated to at least double, ranging from $31 billion to $62 billion.[8]

Although all osteoporosis-related fractures are debilitating, vertebral and hip fractures exert especially profound effects, increasing mortality risks and diminishing quality of life.[9] Individuals with a hip or vertebral fracture experience a 20% excess risk for mortality 5 years after the fracture, with most of the excess mortality occurring within the first 6 months.[4] Moreover, the consequences of an osteoporosis-related fracture can be devastating to the individual's quality of life. For example, 1 year after a hip fracture, 40% of patients are unable to walk independently and 80% are restricted in some activity of daily living, including driving and shopping.[4] Disconcertingly, 27% of post-hip fracture patients enter a nursing home facility for the first time.

The chief goal of osteoporosis management is to prevent fractures. An understand-

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Table 1. Bone Turnover Markers

Formation	Resorption
Total or bone specific alkaline phosphatase (serum)	N-telopeptide (NTX) (urine or serum)
Osteocalcin (serum)	C-telopeptide (CTX) (urine or serum)
Procollagen I extension peptide (serum)	Deoxypyridinoline (urine)

Source: American Medical Association, Osteoporosis Management: http://www.ama-cmeonline.com/osteo_mgmt/module03/01cme/02.htm.

ing of the pathophysiology of osteoporosis provides a foundation that appreciates the role of different therapeutic options in the management of this disorder.

Osteoporosis Pathophysiology

Structurally, bone can be divided into 2 types: cortical bone, the compact and durable outer layer, and trabecular bone, a more delicate interconnected interior latticework. Because trabecular bone displays a greater surface area and is more metabolically active than cortical bone, it is more susceptible to bone loss.[10]

Osteoporosis is a skeletal disorder characterized by bone loss, low bone mass, and structural degradation of bone tissue, especially trabecular bone, yielding attenuated bone strength that, in turn, increases the risk of fracture.[6] Bone strength reflects not only changes in bone density, but also in bone quality—which encompasses bone architecture, the presence or absence of microfractures, mineralization, and bone turnover.[6]

Bone is not inert; instead, it teems with metabolic activity throughout life. After the cessation of linear growth, bone remodeling or turnover—a repeated 120-day cycle of bone resorption including or involving 10 days by cells called osteoclasts followed by 3 months of formation of new bone by cells called osteoblasts—continues through adulthood, maintaining skeletal homeostasis, providing bone elasticity, repairing stress microfractures and producing a steady source of extracellular calcium.[11]

In osteoporosis, bone resorption exceeds bone formation, thus leading to bone loss and increasing skeletal fragility.[11] The bone turnover process results in the release of several key biochemical markers found in either the serum or the urine that reflect either bone formation or resorption (**Table 1**).

Although bone markers reflect bone turnover rates, they are not diagnostic of osteoporosis. However, they may play a role in assessing patients before and during pharmacologic therapy. Thus far, they have not been incorporated into routine clinical practice.[10]

Risk Factors for Osteoporosis and Osteoporosis-related Fracture

Myriad factors have been linked to the development of osteoporosis (**Table 2**).[1]

Once a fracture occurs, the risk for a subsequent fracture increases 2- to 5-fold.[12,13] Both vertebral and nonvertebral fractures increase the risk of a subsequent fracture. Generally, prior fracture, low bone mineral density (BMD), advancing age, female sex, and slender body frame are established risk factors for osteoporosis-related fractures.[14] In addition, the absolute risk for fracture differs notably among ethnic groups. Asian-American women, although manifesting BMD measurements similar to that of white women, have only 32% the adjusted relative risk for fracture.[15] Although the reasons for these ethnic variations are not fully understood, several mechanisms have been proposed, including differences in body mass index (higher in blacks), bone architecture, genetic variations (BMD is highly heritable as a polygenetic trait), and environmental and behavioral influences.[15]

Osteoporosis Diagnosis

The clinical evaluation of the skeletal system includes a medical history, physical examination, laboratory testing, and, if appropriate, BMD testing.

Physical Examination and History. The presence of 1 or more risk factors—older age, previous fracture, low body weight, smoker, menopause, low BMD, family history of osteoporosis, hypogonadism in males,

exposure to glucocorticoids—increase the risk of osteoporosis.[8] The use of glucocorticoids is the most common cause of secondary osteoporosis, especially long-term use of glucocorticoids for disorders such as rheumatoid arthritis and long-term obstructive pulmonary disease.[8] In fact, the risk for excessive bone loss is dramatically increased for any patient receiving orally administered glucocorticoids at a dose equivalent to prednisone 5 mg/day or more for at least 2 months.[6]

Further, the physical examination provides an ideal opportunity to detect manifestations of osteoporosis or vertebral fracture. For instance, height loss can be measured clinically over time. A loss of 4 cm or more would be suggestive of vertebral compression fractures. Moreover, thoracic kyphosis, or "dowager's hump," can indicate the presence of anterior wedge fractures in the thoracic spine.[8]

Biochemical Testing. Several biochemical assessments can be used to exclude secondary causes of osteoporosis (**Table 3**).

For instance, urinary markers indicative of bone resorption can detect changes in the bone remodeling process triggered by hyperparathyroidism, hyperthyroidism, and Cushing's syndrome.[11] Generally, routine laboratory studies are normal in patients with osteoporosis. However, to rule out the possibility of secondary osteoporosis, certain tests should be obtained, including a blood chemistry profile, complete blood count and serum 25-OHD, and thyroid-stimulating hormone levels. Nonroutine or specialized tests may be obtained based on information gleaned from history, examination, or the routine tests already noted.[15]

Bone Strength and Density. Currently, there is no accurate measure of overall bone strength.[6] BMD, a frequently used proxy measurement, accounts for about 70% of bone strength. Operationally, the World Health Organization defines osteoporosis as a T-score—the number of standard deviations above or below the mean BMD for young white adult women—of −2.5 (**Figure 1**). Z-score assessments, in contrast, compare patients' BMD with age, sex, and race-matched controls.

Table 2. Risk Factors for Osteoporosis

Personal history of fracture after age 50
Current low bone mass
Female gender
Being thin or having a small frame
Advanced age
Family history of osteoporosis, especially hip fracture
Estrogen deficiency as a result of menopause, especially early or surgically induced
Primary or secondary amenorrhea
Anorexia nervosa
Low lifetime calcium intake
Vitamin D deficiency
Use of certain medications (corticosteroids, chemotherapy, anticonvulsants, etc)
Presence of certain long-term medical conditions
Low testosterone levels in men
Inactive lifestyle
Current cigarette smoking
Excessive use of alcohol
Caucasian or Asian race

Source: National Osteoporosis Foundation.

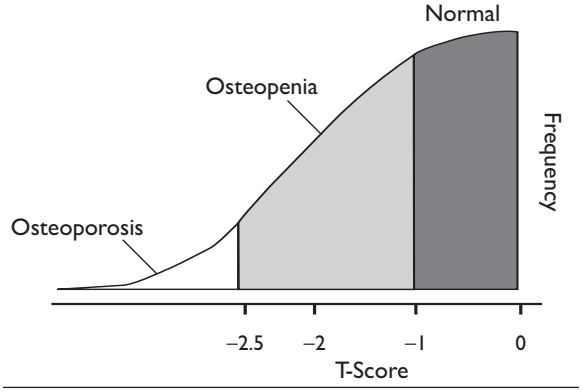
Postmenopausal Women

Ordinary radiographs do not display sufficient sensitivity to diagnose osteoporosis until total BMD has declined by 50%.[15] Consequently, dual-energy x-ray absorptiometry (DXA) has become the most widely used technique for assessing BMD. Because of its precision, central DXA testing has emerged as the diagnostic measure of choice. Peripheral DXA scans of the distal

Table 3. Biochemical Assessments in Osteoporosis

First Level (Routine Tests)	Second Level (Nonroutine Tests)
Chemistry profile	Tissue transglutaminase antibody
25-hydroxyvitamin D	Parathyroid hormone
Carotene	Serum and/or urine protein electrophoresis
Thyroid-stimulating hormone	24-hour urine calcium and creatine
Complete blood count	Urine cortisol Bone biopsy Markers of bone remodeling

Figure 1. WHO Diagnostic Categories for Osteoporosis



WHO indicates World Health Organization.
WHO Guidelines for Preclinical Evaluation and Clinical Trials in Osteoporosis, 1998.

forearm and the middle phalanx have become available and are less expensive than central DXA testing, but the value of these measurements in predicting fracture remains unclear. Central DXA measurements of the spine and hip have the best predictive value for fracture and follow-up monitoring. Quantitative ultrasound has shown promise as a diagnostic tool in osteoporosis but not for follow-up monitoring. Early clinical findings indicate that quantitative ultrasound of the heel can predict hip fracture and nonvertebral fracture almost as well as a DXA at the femoral neck.[6]

Candidates for BMD Testing. There is a consensus that BMD measurements should be considered in patients who have an increased risk for osteoporosis and in all women aged 65 and older.[1,6] The value of universal screening, particularly in perimenopausal women, has not been established.[6] During the perimenopausal period, a large number of women would need to be evaluated and treated to prevent a single fracture. For example, in white women between the ages of 50 and 59 years, an estimated 750 BMD tests would be needed to prevent just 1 hip or vertebral fracture over a 5-year period of treatment.[6] The National Institutes of Health Consensus Panel suggests an individualized approach to treatment in perimenopausal women until solid evidence of the cost-effectiveness of routine BMD screening emerges.

Medicare reimburses BMD testing every 2 years, with exceptions, which reimburse yearly, for the following patient groups[16]:

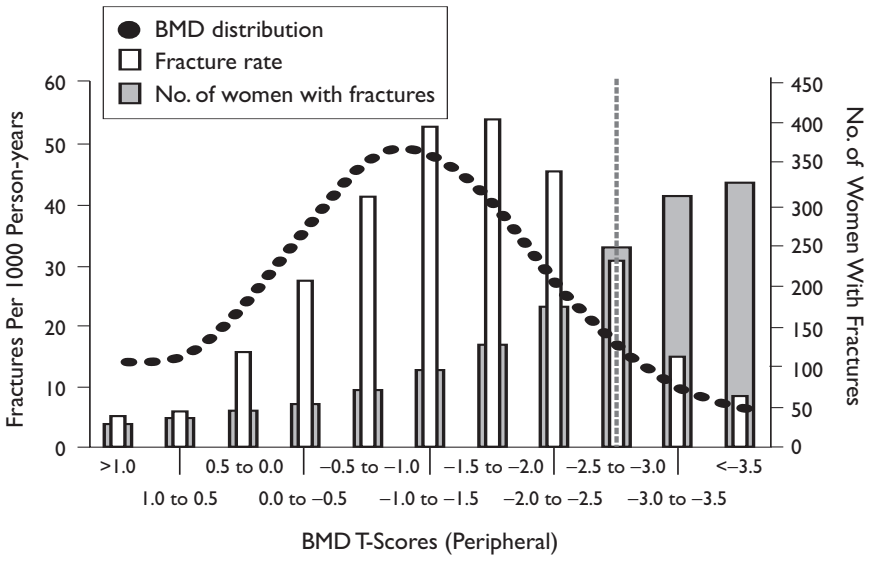
- Estrogen-deficient women at clinical risk for osteoporosis
- Individuals with vertebral abnormalities or osteopenia as demonstrated by x-ray film to be indicative of osteoporosis, low bone mass, or vertebral fracture
- Individuals receiving long-term glucocorticoid (steroid) therapy (yearly)
- Individuals with primary hyperparathyroidism (yearly)
- Individuals being monitored to assess the response to or efficacy of a US Food and Drug Administration (FDA)-approved osteoporosis drug therapy

BMD and Fracture Risk: An Imperfect Relationship

Accumulating evidence from a variety of clinical studies suggests that there is no specific BMD threshold that renders an individual patient "safe" from fracture. The largest study of postmenopausal osteoporosis in the United States, the National Osteoporosis Risk Assessment (NORA) study, which included 200 160 ambulatory postmenopausal women, mean age, 64.5 years, without known osteoporosis, found that almost half the participants displayed low BMD (39.6% osteopenia and 7.2% osteoporosis).[17] Among the participants with follow-up information (163 979 subjects), osteoporosis was linked to a 4-fold increase in fracture rate; yet, even the presence of osteopenia was associated with almost a 2-fold increase in the risk of fractures. A separate analysis of the NORA database that included 149 524 white, postmenopausal women revealed that 82% of the 2259 participants with fractures had T-score >−2.5, suggesting that individuals may experience significant fracture risk with bone density scores that are not in the osteoporotic range (**Figure 2**).[18]

In women, bone loss begins insidiously in young adulthood, proceeds in a linear fashion thereafter and, as bone mass progressively declines, fracture risk increases exponentially.[19,20]

Figure 2. Population-BMD Distribution, Fracture Rates, and Number of Women With Fractures



BMD indicates bone mineral density.
Adapted from Siris ES, et al. *Arch Intern Med.* 2004;164:1108-1112.

Results from the Study of Osteoporotic Fracture (SOF) suggest that in white women over the age of 65 years, a combination of low BMD and other risk factors, such as a previous fracture of any type, treatment with long-acting benzodiazepines or anticonvulsants, previous hyperthyroidism, ingestion of high amounts of caffeine or physical inactivity, yielded a particularly high risk for hip fracture, the risk increasing as the number of risk factors increased.[21] Other investigators have shown that neuromuscular and visual impairments in elderly women (over the age of 75 years), as well as low BMD, are independent risk factors for fracture.[22] These findings highlight the importance of considering other risk factors, such as advanced age and prior fracture, in addition to low BMD, when evaluating an individual's risk for osteoporosis-related fracture. A recent WHO initiative to determine absolute fracture risk or 10-year probability of sustaining a fracture based on key risk factors such as age, prior fracture history, and bone density is under review.

Additionally, the results of numerous clinical studies in osteoporosis suggest that although low BMD is of value in predicting future fractures, increases in BMD in response to intervention do not directly correlate with vertebral fracture risk reduction. Indeed, reduction in fracture risk secondary to antiresorptive therapy occurs early when there is a significant decrease in bone turnover and before a large increase in BMD is evident.[23-29]

Although stable or increased BMD measurements and decreases in bone turnover are important surrogate markers, the clinically important endpoint is reduction in fracture. Indeed, in clinical trials of alendronate, raloxifene, or risedronate, increases in lumbar spine BMD accounted for only a small portion (<20%) of the reduction in risk for vertebral fracture.[30-32] Antiresorptive agents may reduce the risk of fracture through a variety of interrelated mechanisms, including improvements in bone turnover, density, architecture, and mineralization.

Antiresorptive therapies that yield greater improvements in more than 1 of these mechanisms—greater decreases in bone turnover in conjunction with greater increases in BMD—are associated with a reduction in hip and other nonvertebral fractures.[33]

Together, these findings suggest that, in the treatment of osteoporosis, increased

BMD alone is not a clinically meaningful endpoint; reduction in fracture rate remains the desired outcome.

Therapeutic Interventions to Reduce Fracture Risk in Osteoporosis

Over the past several decades major advances have been made in the treatment of osteoporosis based on accumulating evidence from randomized controlled trials. Nonetheless, many women who have had fractures remain untreated. In a retrospective chart review of fracture clinic visits, Hajcsar and colleagues identified 228 patients with fragility fractures, 56% of whom were contacted and agreed to participate in an interview 1 year from the date of fracture.[34] For these mostly female (85%), postmenopausal (77%) patients, follow-up treatment was far less than adequate: 18.5% had received a diagnosis of osteoporosis, 32.4% were prescribed calcium supplementation, 13% were prescribed vitamin D supplementation, and 7.4% were taking bisphosphonates.

General Prevention Strategies. Universal treatment strategies in the management of osteoporosis include counseling all patients on lifestyle management, and emphasizing the importance of adequate daily intake of calcium (1200 mg/day) and vitamin D (400 to 800 IU/day). Calcium and vitamin D favorably modulate age-related increases in parathyroid hormone levels and bone resorption, increase spine and femoral BMD, and reduce vertebral and nonvertebral fracture risk.[6,35] In addition, at-risk patients should be advised to engage in weight-bearing and muscle-strengthening exercises not only to maintain optimal bone maintenance but also to reduce the risk for falls. Patients at risk for osteoporosis should also be advised to avoid tobacco use and excessive alcohol intake, since these activities can accelerate bone loss.[36]

Pharmacotherapy. The National Osteoporosis Foundation advocates initiating pharmacotherapy to reduce fracture risk in women ≥65 years of age with the following characteristics[1]:

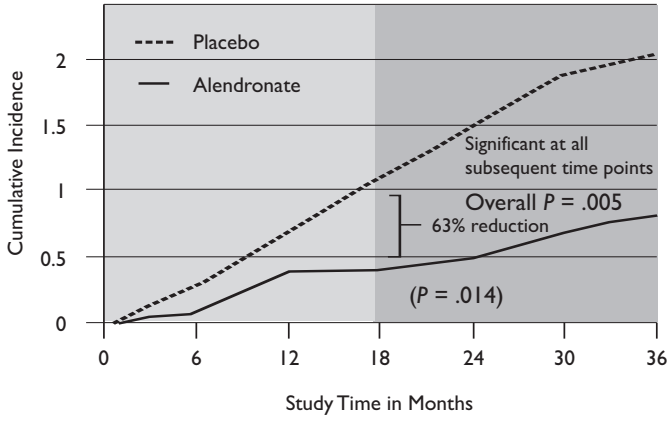
- BMD T-scores <–2.0 by hip DXA with no risk factors
- BMD T-scores <–1.5 by hip DXA with 1 or more risk factors
- A prior vertebral or hip fracture

The current FDA-approved pharmacologic classes for the management of osteoporosis include bisphosphonates, calcitonin, hormone therapy, parathyroid hormone, and selective estrogen receptor modulators.

Bisphosphonates. The bisphosphonates—alendronate, risedronate, and ibandronate—are antiresorptive agents that bind to hydroxyapatite, especially at sites where bone is formed and resorbed, thus attenuating bone turnover and, in turn, bone loss.[37]

Alendronate: In the Fracture Intervention Trial, 3 years of alendronate treatment significantly reduced the risk of vertebral fractures in women with and without baseline vertebral fractures.[28,29] Although not a primary endpoint, alendronate reduced the risk of hip fractures by 51% in women with prevalent vertebral fractures at baseline. The reduction in hip fracture was seen as early as 18 months (**Figure 3**).[28] In posthoc analysis, patients with T-scores <–2.5 or a prevalent vertebral fracture, alendronate reduced the risk of clinical vertebral fractures by 59% after 1 year of treatment. Alendronate has

Figure 3. Incidence of Hip Fracture: Alendronate Versus Placebo



Black DM, et al. FIT. *Lancet.* 1998;348:1535-1541.

also demonstrated a sustained effect on BMD for up to 10 years but the reduction in fractures was not assessed.[38]

Risedronate: In the Vertebral Efficacy with Risedronate Therapy (VERT)–North America study, risedronate significantly reduced the 3-year risk of vertebral and nonvertebral fractures by 41% and 39%, respectively.[26] Vertebral fracture risk reduction was maintained at 5 years, and results after 7 years of risedronate therapy demonstrate a continued low incidence of fracture.[39] Risedronate has also demonstrated a rapid onset of action. At 1 year, vertebral fracture risk was significantly reduced by up to 65%.[26,27] In addition, a pooled analysis of the VERT data and data from other studies indicate a reduction in clinical vertebral, as well as nonvertebral fractures risk as early as 6 months after initiation of risedronate therapy (**Figure 4**).[40,41]

The Hip Intervention Program (HIP) was designed to prospectively evaluate the effect of risedronate on hip fracture risk. After 3 years, risedronate reduced hip fracture risk by 40% in women aged 70 to 79 years with osteoporosis (T-score <–2.5) and by 60% in women with osteoporosis and baseline vertebral fracture.[42] There was a nonsignificant reduction in hip fractures in the older group of subjects in whom osteoporosis was not documented by densitometry measurements. The reduction in hip fracture with risedronate was demonstrated within 6 to 18 months after initiation of treatment (**Figure 5**).[43]

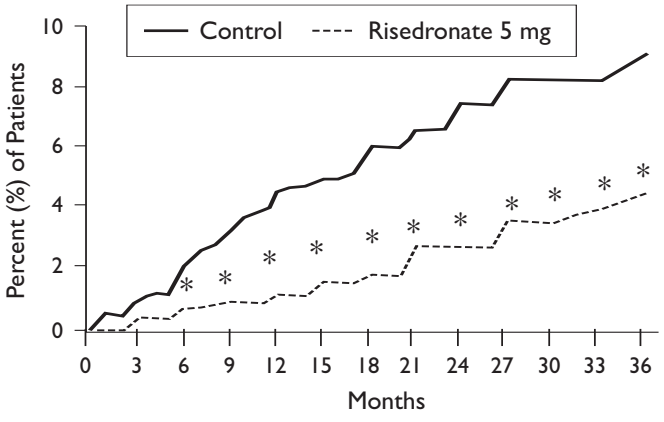
Ibandronate: In a 3-year, randomized, placebo-controlled study that included 2946 postmenopausal women (55 to 80 years of age) with T-scores <–2.5 and >–5.0 with at least 1 previous vertebral fracture, ibandronate, 2.5 mg daily dosing or intermittent dosing with 20 mg every other day for 12 doses every 3 months, reduced the risk for vertebral fractures by 62% and 50% for the daily and intermittent regimens, respectively, when compared with placebo.[44]

No significant differences, however, were detected between ibandronate and placebo in terms of nonvertebral fracture rates. In a noninferiority study, monthly ibandronate, 100 mg and 150 mg, was found to be noninferior in the increases in BMD at spine and hip to daily 2.5-mg dosing.[45] Subsequent analysis showed superiority of the 150-mg monthly regimen to the daily 2.5-mg regimen.

Calcitonin: An antiresorptive agent, calcitonin is indicated for the treatment of postmenopausal osteoporosis in women at least 5 years postmenopausal with low bone mass.[46] The results of a 5-year, double-blind trial found that salmon calcitonin nasal spray (200 IU/day) reduced the risk for vertebral fractures by about a third, but no significant reductions were detected in the risk for nonvertebral fractures.[47]

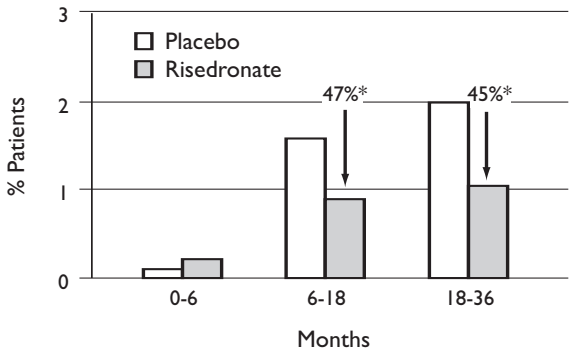
Raloxifene: A second-generation selective estrogen receptor modulator and antiresorptive agent, raloxifene, 60 mg daily for 3 years in women with osteoporosis, has been shown to increase lumbar spine bone density by 2.5%.[48] In addition, in women with osteoporosis or prevalent fractures, raloxifene 60-mg treatment for 3 years decreased the relative risk of vertebral fractures by 30% to 50%, when compared with placebo, but

Figure 4. Risedronate Reduces Nonvertebral Fracture Risk by 6 Months



*$P \leq .05$.
Postmenopausal women with low LS BMD (T-score <–2.5).
Based on a composite endpoint of the following: clavicle hip, humerus, leg, pelvis, and wrist.
LS BMD indicates lumbar spine bone mineral density.
Harrington JT, et al. *Calcif Tissue Int.* 2004;74:129-135.

Figure 5. Onset of Hip Fracture Reduction With Risedronate: Group 1 (Low BMD)



*Relative risk reduction; $P = .05$ versus control.
BMD indicates bone mineral density.
Source: Reference 43.

had no statistically discernible effect on nonvertebral fracture risk.[24]

Teriparatide (1-34 PTH): As a recombinant parathyroid hormone, teriparatide contains the same amino acid sequence as the biologically active portion of endogenous parathyroid hormone and, thus, exerts an anabolic action, building new bone.[49] After 19 months of therapy, once-daily, subcutaneously administered teriparatide (20 µg or 40 µg) reduced the risk for new vertebral fractures by 65% in postmenopausal women with prevalent fractures when compared with placebo (placebo 14% vs teriparatide 5% fracture rate).[50] Moreover, teriparatide treatment resulted in a 50% reduction in at least 1 new nonvertebral fracture over 19 months (placebo 6% vs teriparatide 3%).

Hormone Therapy: Hormone therapy (HT) is a long-established approach for the prevention and treatment of osteoporosis. Recent results from the Women's Health Initiative, which enrolled almost 11 000 postmenopausal women beginning in 1993, found that HT resulted in a reduction of 39%, 38%, and 30% in hip, vertebral, and total fractures, respectively, versus placebo.[51] Unfortunately, a concurrent increase in the incidence of cardiovascular events, chiefly stroke, has cast a serious shadow over the future of HT as an option in the management of osteoporosis.

Conclusions

For managed healthcare, significant opportunities exist for reducing the costs of osteoporosis-related fractures by improving follow-up treatment for fractures and identifying other individuals with osteoporosis at high risk for fracture. Treatment of postfracture patients has been shown to be far less adequate than would be expected in such a high-risk group. Enhanced treatment in this easily identifiable group should yield substantially improved downstream clinical outcomes. A more daunting task, perhaps, is the identification of other groups at high-risk for fracture. BMD, as measured by T-scores, has demonstrated some correlation with fracture risk. Clearly, the preponderance of clinical evidence now requires a consideration of other risk factors—age, prior fracture, glucocorticoid use among others, in addition to BMD, as a means of assessing fracture risk. Administrative claims databases may provide a valuable source of patient information for screening. As a result of the Medicare Modernization Act of 2003, there may be an increased number of patients at risk for osteoporosis enrolling in Medicare Advantage health plans, heightening the importance of effective preventive measures and treatments, with a focus on high-risk populations to improve outcomes. To provide optimal management and cost effectiveness, patients at high risk for fracture will require the use of agents that not only impact BMD but also have demonstrated efficacy in reducing both vertebral and nonvertebral fractures as a major component of a proactive management plan.

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