Osteoporosis
Is There a Rational Approach to Fracture Prevention?

Nancy Lane, M.D.

Abstract
The most effective way to manage osteoporosis is to prevent fractures before they occur. To do this, a clinician needs to be aware of both the clinical risk factors that predispose a patient to an osteoporotic fracture and the patient’s bone mineral density (BMD). An assessment of risk factors that increase fracture risk, including age, weight less than 125 pounds as an adult, family history of hip fracture, low-impact fractures as an adult, inability to rise up from a chair without using one’s arms, presence of rheumatoid arthritis (RA), and use of glucocorticoid medication, in addition to low BMD, is necessary to assess fracture risk. Therefore, a complete history and BMD will improve the identification and treatment of patients at high risk of an osteoporotic fracture. Also, patients with systemic inflammatory diseases like RA or systemic lupus erythematosus have an increased risk of fracture owing to systemic inflammation independent of glucocorticoid use. These patients should be screened for osteoporotic risk factors, and BMD tests should be obtained. Treatment to prevent fractures should be initiated at a BMD (T score) <-1 to improve skeletal health in these patients.

This review provides an update on the epidemiology of fractures, reviews fracture risk-factor assessment, and makes recommendations on how to screen patients and decide which patients would benefit from an intervention. Lastly, this review analyzes the new initiative by the World Health Organization (WHO) to assess fracture risk and new information on assessment of bone health in rheumatic disease patients.

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The most effective management of osteoporosis is to prevent fractures before they occur. The cost associated with the use of medications either to prevent or treat osteoporosis is high, so avoiding unnecessary treatment is a worthwhile goal from an economic point of view. Since such a high proportion of the aging female population will be affected, clinicians need to identify and target osteoporosis treatment for the subset of patients over 50 years of age who are likely to gain the greatest benefit.1,2

Age as a Risk Factor
Peak bone mass usually is achieved in men and women at about 20 years of age. In adult women, bone mass changes little until the onset of menopause when estrogen levels decline, FSH levels increase, and bone is rapidly lost. After menopause women continue to lose bone throughout their lifespan. Therefore, age is a major predictor of osteoporosis (Table 1). When bone mass decreases, whether in the peripheral skeleton or the central skeleton, risk of fractures increases. An increase in the risk of Colles fractures appears first, followed by an increase in the risk of vertebral and hip fractures.

Fracture prevalence continues to increase with advancing age, with a notable increase in women around the age of 75 years and a little later in men. The lifetime risk of an osteoporotic fracture in a 50-year-old white woman is 50%. A woman’s lifetime risk of an osteoporotic fracture is higher than her risk of breast cancer, and is probably similar to her risk of cardiovascular disease. From a clinical perspective, therefore, older women are the most important group to screen for osteoporosis.

T-scores as a Risk Factor
Today, health care providers recommend therapy based mostly on one risk factor, low bone density, meaning a
Table 1  Osteoporotic Risk Factors

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<th>Risk Factor</th>
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<tr>
<td>Age</td>
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<tr>
<td>Weight (for an adult) &lt;125 lb</td>
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<tr>
<td>History of fracture after age 30</td>
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<tr>
<td>Family history of hip fracture</td>
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<tr>
<td>Inability to rise from a chair without using hands</td>
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<td>Rheumatoid arthritis</td>
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<td>Glucocorticoid use</td>
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<td>History of significant smoking and alcohol use</td>
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T-score less than -2.5. The question arises as to whether low bone density by itself is sufficient to identify patients at high risk of a fracture and to justify the cost of pharmacologic therapy.

In 1992, the World Health Organization (WHO) developed bone density threshold criteria for the diagnosis of osteoporosis: 2.5 standard deviations below peak bone mass. Soon after the WHO report, physicians began to use a T-score below -2.5 as a diagnostic criterion for osteoporosis. However, using T-scores alone has an inherent shortcoming, as bone density is a continuous variable and fracture risk is a continuous outcome. The correlation between them is far from one-to-one. Patients with T-scores above -2.5 can have fractures, and some patients with T-scores below -2.5 do not have fractures. T-scores do not provide an absolute prognosis. Bone density is important, but it does not explain all of an individual’s risk of fracture.

Numerous observational studies have reported that up to half of the patients with incident fractures have baseline BMDs that are above the WHO diagnostic threshold of osteoporosis, with T-scores between -1 and -2.5. This suboptimal range is defined as osteopenia. However, very few studies have evaluated osteoporotic fracture risk in individuals with T-scores on the low side of the norm, that is between 0 and -2.5. The National Osteoporosis Risk Assessment (NORA) study assessed this population. This study enrolled approximately 200,000 postmenopausal women across the United States who did not have a diagnosis of osteoporosis, had not had a BMD scan, and were not undergoing osteoporosis therapy. A questionnaire provided information on osteoporosis risk factors, and measurements of peripheral BMD were obtained. The number of fractures was highest in women with osteopenia who were between the ages of 50 and 59. Interestingly, patients who had osteopenic T-scores and were below age 60 in that year had a 12% risk of having a fracture. Therefore, osteoporotic fractures occur in patients who do not qualify as having “osteoporosis” by the WHO guidelines. Yet the US Public Health Service does not recommend screening people under age 60 for BMD.

The results of the NORA study have been criticized as irrelevant to clinical practice because noncentral measurements of BMD were obtained and because it was funded by a pharmaceutical company. However, a longitudinal study of elderly Caucasian women (Study of Osteoporotic Fractures [SOF]) had similar findings. In this study of osteoporotic fractures, women 65 years or older were recruited to evaluate risk factors for osteoporosis. Women who had T-scores greater than -2.5 at the baseline visit accounted for 54% of the hip fractures and 74% of all nonvertebral fractures over a 10-year follow-up period. In a large European cohort of elderly men and women from Rotterdam, the majority of the fractures occurred in patients with T-scores above -2.5. Since patients with BMD scores above -2.5 can have fractures, clinicians need to know which clinical risk factors, in addition to BMD, help to stratify risk for fracture. The clinical risk factors that identify individuals at risk for osteoporotic fractures include: a prevalent fracture, a fracture as an adult, a parent having a hip fracture, low weight or weight loss, smoking, glucocorticoids, difficulty rising up from a chair without using one’s hands, and disability.

The risk factors that modulate or attenuate the relationship between BMD and fracture can be quantified by age (as age increases in increments of 5 years over the age of 65, risk increases by 50%), weight (decrease in weight by ≥20% after age 25, and family history (a mother with a history of hip fractures and existing vertebral fracture doubles the risk in white women).

Vertebral Fracture as a Risk Factor

What about a prevalent vertebral fracture? In the Fracture Intervention Trial, 8% of women with a prevalent vertebral fracture at the study initiation had new fractures within 3 years versus those in the control group that did not have baseline fractures. In another large phase 3 randomized placebo controlled trial of raloxifene for the treatment of osteoporosis, the Multiple Outcomes of Raloxifene Evaluation (MORE) study, 13% of placebo-treated patients with a prevalent vertebral fracture at baseline suffered a new fracture over the next 3 years. Therefore, prevalent osteoporotic fracture identifies a group of patients at high risk for another fracture (Table 1). Identifying this group of “high risk” fracture patients is critical.

Biochemical Markers as a Risk Factor

In 2000, participants in a consensus conference on osteoporosis redefined osteoporosis as a disease of reduced bone strength. They defined bone strength as bone mass plus other bone qualities, including micro-architecture, bone remodeling, bone turnover, mineralization, bone size and shape, and other factors that are more difficult to quantify, such as damage accumulation. One component of bone quality that is related to fracture and that can be measured quantitatively is bone remodeling. Garnero and colleagues evaluated a population of elderly women in France and divided the women into the following groups: low bone mass, high bone mass, low turnover, and high...
turnover, as measured by serum alkaline phosphatase. While low bone mass increases the risk of a fracture to about 2.5 times that in women with normal bone mass, a high level of the bone trial marker alkaline phosphatase increased risk to about the same degree. However, when low bone mass, high bone turnover marker, and a history of prior fracture were combined, the hazard ratio doubled to 5.3 compared to the normal bone mass and turnover group. Garnero’s group repeated these analyses in the Epidemiology of Osteoporosis (EPIDOS) study. The investigators evaluated patients at baseline and followed them for 22 months. Women with low total hip bone mass had a 2.5-fold greater risk of a hip fracture than patients in the control group. Individuals who had a high bone turnover, as measured by osteoclast markers, had risk increased by about twofold. However, in the group of women with low bone mass and high bone turnover, the risk of the hip fracture increased nearly fivefold compared to patients with normal bone mass and low turnover.

Another study evaluated the utility of baseline biochemical markers of bone turnover for predicting future fractures. Siebel and colleagues evaluated baseline serum markers from a randomized controlled trial that evaluated risedronate versus placebo for osteoporosis. The investigators divided the patients by baseline urine deoxypyridinoline levels below and above the median value. After 1 year of follow-up, patients who were above the median for a high turnover had about an 8% risk of a new vertebral fracture compared with those patients below the median level of the bone turnover marker. Next, the investigators evaluated the effect of risedronate on vertebral fracture risk reduction and found that risedronate produced a greater fracture risk reduction in the high turnover group compared to the low turnover group. These studies confirm the relationship of bone turnover markers to fracture risk as well as their importance in deciding whether to treat pharmacologically.

How to Assess a Patient’s Risk of Osteoporotic Fracture

Black and colleagues have developed and validated a simple-to-use index to assess risk for osteoporotic fractures. Variables making up the index include age, history of a broken bone after age 50, history of mother having a hip fracture after age 50, weight less than 125 pounds, current smoker, need to use hands/arms to get out of a chair, and BMD T-score (Table 1). The scoring is straightforward: 1 point per decade above 65 up to a maximum of 5 points for age; 1 point for ever having broken a bone; 1 point if the mother had a hip fracture, 2 points if the patient uses hands/arms to assist rising from a chair. BMD measurement of the hip of -1 to -2 is given 2 points, -2 to -2.5 is given 3 points, and -2.5 or less is given 4 points. Using osteoporotic fracture data from the SOF, the index was found to predict an 8% risk of hip fracture within 5 years if the total score was 5 points versus less than 1% risk within 5 years for patients with low scores. Bone density measurements were not critical to risk prediction. However, the SOF only evaluated elderly Caucasian women from the United States; therefore the validation may not have wide-ranging applicability.

Indices to predict fracture risk are not new. In 1995, Cummings and coworkers reported that both low bone density and clinical risk factors predict fracture risk. Including more predictors than just low bone density improves the ability to predict risk. The more risk factors a patient has for fracture with low bone density, the greater the risk of fracture (especially hip fracture).

WHO Analysis

The WHO scientific group recently convened to develop more ways to assess fracture risk. This project is ongoing, and the group plans to develop a standardized methodology for expressing fracture risk and intervention threshold for men and women. John Kanis is the head of this intensive project. The rationale for this initiative is that T-scores are insufficient to predict fracture risk. Therefore, the group will use a number of methods, including meta-analysis, mega-analysis, validation, and country-specific incidence rates to develop country-specific intervention thresholds.

The T-score has many good attributes: it is simple and widely used, it has good correlation with fracture risk, and it can detect some high-risk patients. However, shortcomings to the T-score include: lack of standardization of which skeletal sites to evaluate, lack of generalization to non-Caucasian groups, and use of BMD as the only risk factor for osteoporosis evaluated. Inappropriate T-score thresholds for osteoporosis treatment have incorrectly identified patients who do not in fact have a high risk of fractures.

The WHO initiative methodology currently being tested does not treat all osteoporosis risk factors equally. The simple version is the hip T-score plus age. An expanded version will include additional risk factors, and there will be a limited BMD version. For Third World countries that do not have bone density measurement readily available, there will be a non-BMD version, which will include only clinical risk factors. Intervention thresholds will be recommended, which may be complicated. The proposal is to develop hip fracture equivalents weighted for fragility fractures, and to use. A hip fracture in a 50-year-old woman would be equal to 2 vertebral fractures, which would be equal to 4 humerus fractures. For example, a 65-year-old woman in Sweden would be treated if she has a 4% 10-year hip fracture risk equivalent, assuming a number of factors in the model. Intervention thresholds will be set by the global cost-effectiveness model. This will allow each individual country to determine how to
Many guidelines—more than 21 by recent count—are available today. There is general agreement to treat older patients with osteoporosis, but no consensus has developed about other at-risk groups. Most clinical guidelines do not distinguish between BMD-independent and BMD-dependent risk factors, and no currently published guidelines use fracture probability.

Patients With Rheumatic Disease

Patients with inflammatory/rheumatic diseases have an increased risk of osteoporosis (Table 1). The WHO recognizes this by listing RA as one of the major risk factors. In their review of inflammatory bone loss in RA, Gravalese and Goldring noted that the synovium and the T cells release proteins that activate osteoclasts and reduce osteoblast activity, setting up a very aggressive, almost malignant, bone remodeling. RANK-ligand/OPG ratio changes and RANK-ligand increases are very potent stimulants of inflammatory bone loss, both localized and generalized. Orstavik and colleagues evaluated 250 RA patients and 150 age-matched controls. RA patients were similar to controls: they were somewhat older, weighed somewhat less, and their Health Assessment Questionnaire (HAQ) scores were somewhat higher. However, nearly 30% had two or more vertebral deformities compared to those without RA. The vertebral deformities in these RA patients occurred despite their T-scores being very close to normal. Therefore, skeletal fragility in RA is present even with a relatively normal BMD.

Borba and colleagues evaluated patients with systemic lupus erythematosus (SLE) (n=31) and controls (n=32) who were younger than 40 years old. Twenty percent of the lupus patients had vertebral fractures in the spine with normal BMD. Similarly, Bultink and colleagues reported on 107 SLE patients, mean age 41 years, observing that 39% had low bone mass, 20% had prevalent fractures, and only 4% had true osteoporosis. Therefore, fractures occur in RA patients with normal or modestly low BMD. Systemic inflammation can significantly alter bone turnover by reducing osteoblast activity, while dramatically increasing osteoclast activity. Therefore, it is not surprising that rheumatic disease patients with systemic inflammation and relatively normal bone density have increased risk of fractures.

Patients with inflammatory rheumatic diseases, ranging from arthritis to vasculitis, have a high risk of fracture independent of their BMD. Therefore, a more aggressive approach to diagnosis and treatment is required to reduce fracture risk in these patients. A BMD measurement in rheumatic disease patients is mandatory. If a patient has ankylosing spondylitis, a hip BMD is needed rather than a spine BMD. Young patients require treatment to augment their achieved peak bone mass, first with calcium and vitamin D for good skeletal health. Reduction of their systemic inflammation is needed to lower their fracture risk. The threshold for using antiresorptive agents or bone active agents in rheumatic patients should be low. Therapy can be instituted for patients with T-scores of -1 or below, or those with clinical risk factors. In younger patients, the clinical risk factor may be low-trauma fracture as an adult. These patients need attention to their skeletal health as well as their inflammation, because compared with postmenopausal women, patients with rheumatic diseases have a higher fracture risk.

Conclusions

Both bone mass and a history of clinical risk factors should be taken into consideration in identifying individuals at the highest risk for osteoporotic fractures. In addition, patients with rheumatic diseases and systemic inflammation are at a very high risk of osteoporotic fractures, despite being young and having relatively normal bone mass measurements. Patients with rheumatic diseases should be screened for osteoporotic risk factors, screened with BMD measurements, and treated to prevent osteoporotic fractures at bone mass levels (e.g., T-scores <-1).

References


