Chapter 8: Key Messages

- Much of the burden of bone disease can potentially be avoided if at-risk individuals are identified and appropriate interventions (both preventive and therapeutic) are made in a timely manner. The evidence suggests that health care providers frequently fail to identify and treat individuals at high risk for future osteoporosis or other disorders of bone, even those who have already had a fracture.
- It is important to evaluate the risks for poor bone health at all ages. Therefore, assessment of calcium and vitamin D intake, physical activity, and adverse behaviors such as smoking should be a routine part of health care for all individuals.
- Those in greatest need should receive a full assessment of bone health. Diagnostic methods are available that can help to identify those in the population who are at highest risk of fracture.
- Both the public and health care professionals need to be aware of a number of known, easy-to-identify risk factors for osteoporosis and other bone diseases.
- Providers should be aware of a number of red flags that might signal potential problems with an individual's bone health at different ages. One of the most important flags is a previous fragility-related fracture.
- While osteoporosis is clearly the most common bone disease, health care providers must also actively look for other bone diseases. Diseases such as hyperparathyroidism, rickets, osteomalacia, and Paget's disease can often be identified by being aware of the warning signs and/or through simple biochemical measurements. Early identification of such diseases is critical, since treatment at an early stage can often be highly effective.
- Bone mineral density or BMD testing should be performed on any patient for whom risk factor analysis indicates a strong potential for osteoporosis. Formal guidelines have been developed recommending BMD testing in certain populations, including postmenopausal women over age 65, younger women with multiple risk factors, and men and women with fragility fractures or who have other diseases or take medications that can greatly increase the risk of fracture.
- Individuals who are diagnosed with osteoporosis should be further assessed for secondary, treatable causes of the disease, particularly men and premenopausal women who suffer a fragility fracture.

Chapter 8

ASSESSING THE RISK OF BONE DISEASE AND FRACTURE

While individuals undoubtedly can do a great deal to enhance their bone health through appropriate lifestyle choices, health care professionals play an important supporting role in helping their patients to maintain strong, healthy bones throughout life. In addition to providing education about nutrition, physical activity, and other bone-healthy behaviors, health care professionals also need to assess the risks of bone disease and fracture in their patients and to identify and intervene with those at greatest risk.

In an optimal health care environment, expensive diagnostic tools and treatment interventions should be targeted at those who are at increased risk of a particular disease or condition. The challenge is to find simple ways to identify individuals in greatest need of more careful assessment. Thus, in contrast to the public health approaches to bone health in areas like nutrition and physical activity (which can be aimed at the entire population), this chapter discusses the tools available to identify and intervene with those in the population who are at highest risk of fracture.

As discussed in previous chapters, osteoporosis and other bone disorders represent a large burden for society and for individuals. Billions of dollars are spent each year to treat bone-disease-related fractures that often result in reduced function and quality of life. At worst, fractures start a downward spiral in health that can ultimately lead to severe disability or even death. Much of this burden can potentially be avoided if individuals who are at risk of bone disease are identified and appropriate interventions (both preventive and therapeutic) are made in a timely manner. Yet there has been relatively little focus on these strategies in this country. There are many studies documenting the failure to identify and treat individuals at high risk for fractures or other disorders of bone, even those who have already had a fracture (Solomon et al. 2003, Andrade et al. 2003, Kiebzak et al. 2002, Kamel et al. 2000, Feldstein et al. 2003). In a recent study of four well-established midwestern health systems, only one-eighth to a quarter of patients who had a hip fracture were tested for their bone density, fewer than a quarter were given calcium and vitamin D supplements, and fewer than one-tenth were treated with effective antiresorptive drugs (Harrington et al. 2002). The failure to diagnose and treat bone disease in many high-risk patients has serious implications, as the risk of future fractures is greatly increased in patients who have had a previous fragility fracture, especially in the first year or two after the fracture (Johnell et al. 2004).

Management of bone disease requires the appropriate application of current knowledge concerning the prevention, diagnosis, and treatment. Those patients who have "healthy" bones should be advised about appropriate steps to take with respect to prevention. Those who are "at risk" for bone disease (e.g., those with low bone mass and other risk factors) should be evaluated further, advised about appropriate prevention, and considered for treatment. Those with established bone disease should be advised about secondary prevention (e.g., ways to avoid first or repeat fractures) and be put on appropriate treatment. They should also be evaluated for so-called "secondary causes"—that is, diseases and drugs that can aggravate or even cause osteoporosis.

None of these activities can occur without implementation of strategies for assessing the risk of bone disease in a given patient. This assessment process helps to "sort" patients into different categories of risk, which in turn helps to determine appropriate next steps with respect to prevention, further diagnosis, and treatment. This chapter describes this assessment process, providing details on the best approaches to assessing bone health and diagnosing bone disease. It is important to remember that all of the many factors that can increase fracture risk should be considered in evaluation of the individual patient.

Step 1: Identify At-Risk Individuals Who Require Further Evaluation

The first step for health care providers in assessing individuals is to identify the relatively small number of younger individuals (out of the majority of individuals who do not have bone disease) who require further evaluation. This initial assessment ensures that more extensive (and expensive) testing is reserved for those who likely need it. This multi-pronged process is described below.

Consider Potential Risk Factors for Bone Disease

Although there is a great deal more that needs to be discovered about which risk factors are most important for deciding to measure bone mineral density (BMD) in younger men and women (i.e., those for whom BMD is not recommended because of age alone), enough information already exists to dramatically improve diagnosis, prevention, and treatment of bone disease. That information needs to be applied more broadly by health care professionals.

Both the public and health care professionals need to be aware of a number of known, easy-to-identify risk factors for osteoporosis and other bone diseases. These factors relate to either the intrinsic strength of bone or the propensity to suffer injurious falls. Yet it is remarkable how often these signals are ignored in busy practice settings. All individuals, young and old, should be assessed to determine how many (if any) of these risk factors they have, and then those with a sufficient degree of risk need to undergo further evaluation (often a BMD test) to determine the appropriate next course of action (e.g., changes to lifestyle, pharmacologic treatment). If these steps are taken, much can be done to decrease the burden of bone disease in the population, and much illness and suffering can be avoided. This risk factor analysis is also critical in ensuring the efficient use of health care resources, helping to identify those at-risk individuals in need of BMD testing and potentially treatments without the need for expensive, universal screening. Finally, it is important to remember that bone

"Twelve thousand people come through our [health system's] doors with osteoporosis and we never notice them."—Health system physician

Men Can Get Osteoporosis, Too

This story demonstrates the importance of not forgetting that men can also get osteoporosis, even at a relatively young age. It also highlights the need for the medical profession to become aware of the potential for severe osteoporosis to develop in younger men.

This college professor first fractured his ankle as a young man. The doctor told him he might have "a little osteoporosis" and recommended that he take calcium to strengthen his bones, but did not test for osteoporosis. It was not until years later, after many warning signs, that he finally received a bone density test that showed severe osteoporosis. At that time he was placed on bisphosphonates, a treatment that he continues today. The bisphosphonates have helped him to regain some bone density. His BMD is presently stable, albeit at a very low level. Osteoporosis has had a profound effect on his life. He is constantly afraid of falling, and as a result seriously curtails his activities (e.g., he gave up running).

"Where in the heck were the doctors? I had a slew of warning signs but no one picked them up." —Male with severe osteoporosis

Not Just a Disease of the Elderly

This woman's story illustrates the need of the medical profession to be aware of the warning signs of bone disease in younger individuals and to be aware of appropriate treatments for the disease in this population.

This woman began suffering bone fractures while still in her 30s. Even as pain levels increased and her quality of life suffered, her doctor blamed her problems on clumsiness. After she turned 40, her internist attributed her problems to being a natural consequence of "getting old." Finally, after breaking her ankle at age 43, an orthopedist diagnosed osteoporosis. At this point she had lost bone mass and was shorter than earlier in life, probably due to spine fractures. The doctor told her there was no treatment available for osteoporosis. He advised her to take calcium supplements and to exercise, although he provided no guidance on what types of exercises would be helpful and safe. While she had a long list of "don'ts" with respect to her life, she did find that exercise made her feel better. Yet she remained paralyzed with fear, particularly after her physician gave her the following advice: "above all else, don't fall." Today, at age 55, she has finally turned the corner on the disease. Thanks to medical treatment, calcium supplements, and exercise, her bone mass has improved. She is no longer considered to have osteoporosis, but rather is classified as osteopenic (i.e., she has low bone mass).

"People with osteoporosis do not just die; they slowly break apart."
—Long-time osteoporosis sufferer

health can be compromised at any age, and thus the risks for poor bone health should be evaluated in individuals of all ages. Assessment of calcium and vitamin D intake, physical activity, and adverse behaviors such as smoking should be part of health care for all.

Be Aware of "Red Flags" That Signal Need for Further Evaluation

There are a number of "red flags" that might signal potential problems with an individual's bone health at different ages. Specific problems at different stages of life are discussed in Chapter 10. These "red flags" apply to both men and women. Indeed they may be particularly important to keep in mind in men and Black women, since they are often not considered to be at high risk for bone disease. One of the most important flags is a previous fragility-related fracture, as such a fracture is one of the strongest indicators that an individual may have osteoporosis or some other metabolic bone disease (Ettinger et al. 2003, Haentjens et al. 2003). Any individual with a history of fractures related to only mild or moderate trauma (e.g., a fall from standing height or less) should be assessed further for the potential for bone disease. Yet most are not adequately evaluated today. Another important flag relates to family history of the disease, since there is a component of heredity not only in osteoporosis, but also in Paget's disease and hyperparathyroidism as well as congenital disorders such as osteogenesis imperfecta. Thus, both the public and health care professionals should be alert to looking for other family members who have bone disease. This type of family case finding can and should lead to earlier diagnosis and treatment. The presence of certain bone diseases (e.g., Paget's disease) should be a flag for other family members to be screened, or for screening for associated disorders (e.g., a patient with hyperparathyroidism who has other family members with the disease should undergo genetic screening for other associated endocrine disorders, such as multiple endocrine neoplasia syndromes, familial conditions in which patients may develop tumors of several endocrine glands).

"Red Flags" That Warrant Further Assessment for Osteoporosis or Other Bone Diseases

- History of fractures related to mild or moderate trauma (e.g., a fall from standing height or less)
- Family history of bone disease
- Low body weight
- Weight loss of more than 1 percent per year in the elderly
- Late onset of sexual development
- Unusual cessation of menstrual periods
- Anorexia nervosa (often related to marked weight reduction)
- Athletic amenorrhea syndrome (related to intense physical activity)
- Patients being treated with drugs that affect bone metabolism (e.g., glucocorticoids)
- Patients with diseases linked to secondary osteoporosis (see Chapter 3)
- High levels of serum calcium or alkaline phosphatase in otherwise healthy patients
- Hyperparathyroidism, hyperthyroidism, or treatment with high doses of thyroid hormone
- Height loss or progressive spinal curvature

Low body weight is another important "red flag" signaling the potential for osteoporosis; low body weight is associated with lower BMD and

greater bone loss, even in premenopausal women (Bainbridge et al. 2004). Moreover, weight loss of more than 1 percent per year in the elderly is associated with more rapid bone loss and increased risk of fracture (Hannan et al. 2000, Knoke et al. 2003, Ensrud et al. 2003).

There are other potential flags as well. While bone disease is rare in children, the possibility of congenital disorders should be considered when children fracture, particularly with little trauma. In adolescents, health care professionals should consider abnormalities of sex hormone function, particularly at puberty, to be a potential risk factor, along with late onset of sexual development or loss of sexual function with cessation of menstrual periods. This is often related to marked weight reduction, in anorexia nervosa, or to intense physical activity, in the athletic amenorrhea syndrome. Individuals of all ages with calcium and vitamin D deficiency or prolonged immobilization and paralysis should also be carefully evaluated, as should those who have other diseases that increase the risk of bone loss and fractures, including gastrointestinal and kidney disorders and arthritis. Those patients being treated with drugs that affect bone metabolism (e.g., glucocorticoids) should also be considered as potentially being at risk. Finally, patients already diagnosed with osteoporosis should be screened for secondary, treatable causes of the disease, especially in men or premenopausal women who suffer fragility fractures. Diseases linked to secondary osteoporosis (see Chapter 3) are relatively uncommon in the population, but they can have a devastating effect on the bone health of the patients with these conditions and consequently may require specific treatment.

It is important to remember that not all the "red flags" point to osteoporosis, and that some may be an indicator of other types of bone disease. It is important to look for these diseases. For example, increased levels of serum calcium and alkaline phosphatase in blood are often found by routine screening, yet abnormal values are often ignored (Murff et al. 2003). High serum calcium concentration in an otherwise healthy patient most often indicates primary hyperparathyroidism, although many other causes of hypercalcemia need to be considered. Low serum calcium concentrations are less common but can occur in individuals with vitamin D deficiency and malabsorption. Hypocalcemia is also commonly seen in seriously ill patients and frequently is associated with increased severity of illness or death. Apparent hypocalcemia can be due to low serum protein concentrations, and hypercalcemia can be masked by such low concentrations. Patients with Paget's disease are often identified by the finding of a high serum alkaline phosphatase before there is evidence of bone pain or before the skeletal lesions have actually been detected. (Elevated serum alkaline phosphatase levels are often caused by other problems, particularly liver disease.) Such findings are important because treatment can be highly effective for these and other bone disorders if they are diagnosed early.

Suspicion of vitamin D deficiency (e.g., due to low intake, little exposure to sunshine) is another "red flag" that signals the need for further evaluation. This deficiency is common in the elderly, particularly individuals living in northern latitudes. Assessment of vitamin D deficiency can be accomplished by measuring the most abundant circulating form, 25-hydroxy vitamin D. This measurement should be carried out in individuals who are at high risk of deficiency, including those with evidence of gastrointestinal disorders that might result in malabsorption. Measurement of serum phosphorus is generally not critical in

assessing bone health, but if the levels are low this may be an indication of hyperparathyroidism or vitamin D deficiency. Finally, high blood calcium levels can serve as a "red flag" that potentially indicates primary hyperparathyroidism, and PTH should be measured in all such patients. PTH measurements are also helpful in assessing the extent of secondary hyperparathyroidism in patients with calcium and/or vitamin D deficiency and in those with renal disease.

Consider Use of a Formal Assessment Tool to Determine the Need for BMD Testing

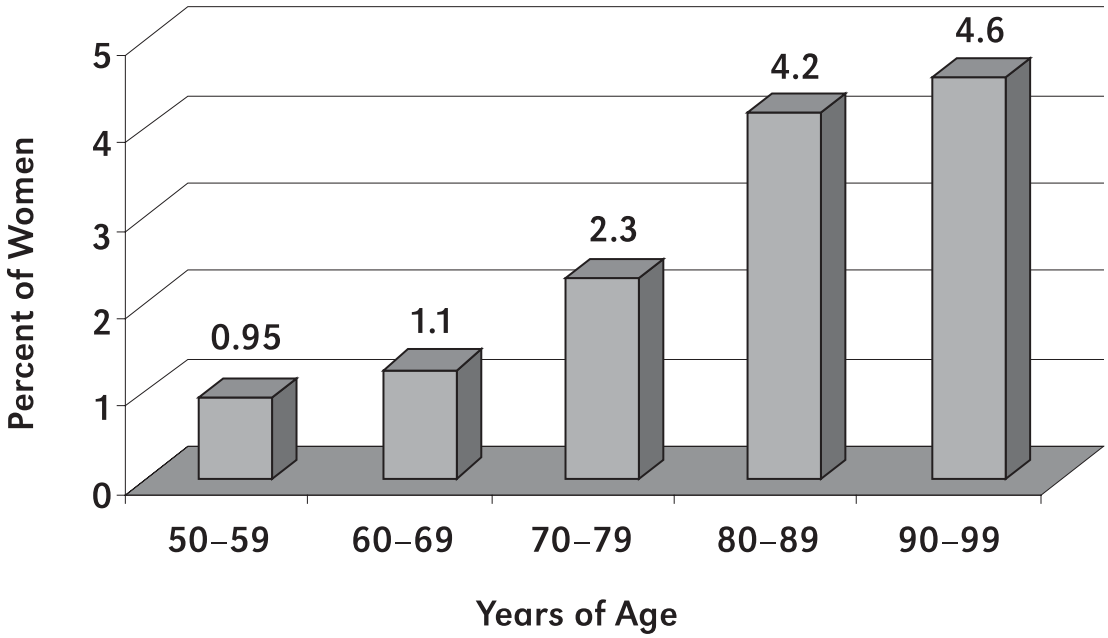
BMD testing still serves as the "gold standard" diagnostic test for identifying osteoporosis and fracture risk. As noted, population-wide BMD testing is not a cost-effective or practical method for assessing the risk of bone disease. While BMD testing has been recommended for some populations (women over age 65), BMD tests are not routinely used for other individuals, the vast majority of whom do not have and are not at risk for bone disease. Widespread BMD testing makes little economic or medical sense. Rather, as noted, the evidence supports the assessment of other risk factors first, in order to identify a subset of at-risk individuals who are most likely to benefit from the test (e.g., younger women with multiple risk factors and both men and women who have had fragility fractures or who have diseases that can greatly increase fracture risk). Some of these risk factors may act directly or indirectly to affect BMD levels, but others are independent of bone density (e.g., risk factors for falling).

Existing clinical recommendations (NOF 2003) already make use of universally accepted risk factors, such as gender, age, and history of spine fracture, in determining who should get BMD testing. Since age is a major determinant of fracture risk, many groups have recommended that BMD measurements be obtained in all White women over age 65 (age is a risk factor, see Figure 8-1) and for younger postmenopausal women with additional risk factors. It is interesting to note that treatment recommendations are also based on these risk factors, as treatment is recommended not only for those with low BMD, but also for those with an existing (especially recent) low-trauma spine fracture, regardless of BMD.

There is great interest in developing a screening tool or "clinical prediction rule" based on risk factors that can easily be assessed clinically (e.g., height and weight) or by patient report (e.g., personal or family history of fracture). The goal of a risk factor assessment tool is to produce a more individualized approach to diagnosis and treatment for all age, gender, and ethnic groups. Ideally, nurses and other nonphysician health care professionals should be able to administer the tool (e.g., by having a patient fill out a short questionnaire) and interpret the results, thus allowing someone other than the busy physician to play a lead role in identifying at-risk individuals.

A number of risk-factor assessment tools are in various stages of development. While there are some problems and limitations with each of these tools (see text box), progress is being made. The National Osteoporosis Foundation (NOF) checklist, for example, may be suitable for individual self-assessment. Individuals can use this checklist and discuss any concerns about their bone health at their next medical encounter. The Osteoporosis Risk Assessment Instrument (ORAI) calculates scores based on age, weight, and current estrogen use; it has a sensitivity of 93 percent—i.e., it identifies 93 percent of the people with low BMD—and specificity of 39 percent—i.e., 61 percent of the people identified

Figure 8-1. 5-Year Hip Fracture Rates for Women with T- score of –2 Without Previous Hip Fracture, by Age



Note: This figure shows that a 90-year-old woman with a T- score of –2 has a 4.6-fold higher risk of having a hip fracture than a 50-year-old woman with the same T-score. Age is an important and independent determinant of fracture risk.

Source: Adapted from Nelson et al. 2001.

do not have low BMD (Cadarette et al. 2000; Cadarette et al. 2004). The Simple Calculated Osteoporosis Risk Estimation (SCORE) considers six risk factors—age, race, weight, estrogen use, rheumatoid arthritis, and personal fracture history—and has a sensitivity of 91 percent and specificity of 40 percent (Lydick et al. 1998), results that are quite similar to the ORAI tool. The Osteoporosis Self-Assessment Tool (OST) uses only two risk factors—age and weight—and also has similar sensitivity (92 percent) and higher specificity (46 percent) (Geusens et al. 2002, Richy et al. 2004, Cadarette et al. 2004). A score based on age, body weight, and fracture history was recently developed from the Dubbo Osteoporosis Epidemiology Study; it performed well in predicting low BMD, but not fractures (Nguyen et al. 2004). Finally, NOF

Problems and Limitations With Existing Tools

Some problems and limitations have slowed the development and widespread application of risk-factor assessment tools. One important issue relates to limitations of current medical knowledge about risk factors for bone health. While epidemiologic (large population) studies have established the importance of age, gender, and ethnic characteristics as important clinical predictors, there is still considerable uncertainty about which clinical characteristics to include in a risk-factor assessment tool. An important problem stems from limitations in the studies evaluating risk factors; they have been relatively well studied in older (over age 65) White women, but less well studied in other groups. It is possible that the importance of particular factors may differ between women and men, people of different races, and younger and older individuals. To date, the generally accepted risk factors for bone loss account for only one-third to one-fifth of the differences in BMD between individuals (Orwoll et al. 1996). Thus, it is clear that important risk factors remain to be discovered. In fact, one potential risk factor that has not been included in any of these instruments is height loss. While loss of height and curvature of the spine may not be related to bone health (they can be caused by poor posture, decreased muscle strength, or narrowing of the intervertebral discs (Ettinger et al. 1994, Coles et al. 1994, Balzini et al. 2003), they could be a sign of osteoporosis. Substantial height loss (more than one inch) and new spinal curvature should serve as a red flag that alerts health care providers to the possibility of vertebral compression fractures (Huang et al. 1996, Ensrud et al. 1997, Vogt et al. 2000). Providers should also consider tracking changes in height as a means of monitoring the impact of preventive and therapeutic measures for osteoporosis. One problem with this approach is that height loss is difficult to assess because an individual's memory of previous height can often be inaccurate, as can current height measurements. To overcome this problem, the use of specific devices for accurate measurement of height and spinal curvature (stadiometers and kyphometers) may be appropriate in specialty clinics.

practice guidelines consider age, weight, current cigarette smoking status, family history of fracture, and personal fracture history, but have not defined any specific scoring system (Johnston et al. 1998). Any of these approaches might be used in clinical practice to determine who would benefit from BMD testing. Examples of some of the most simple and useful of these tools appear in Chapter 10, including those that a busy clinician or patient could use to assess risk factors and determine if a BMD test is indicated.

Efforts have also begun to expand clinical risk assessment tools beyond the question of who should get a BMD test. Tools are being developed to assess not just the risk of low BMD, but also the risk for fractures (which is ultimately what we are trying to prevent). Individuals identified as having a high risk of fracture can be targeted for early intervention. A recently developed tool allows for a more global assessment of risk factors. The risk factors used to develop this tool were derived from the large "Study of Osteoporotic Fractures" (Cummings et al. 1995). This study identified numerous risk factors for hip fracture in elderly White women that are independent of BMD or personal

fracture history (see Table 8-1). These risk factors relate to genetic influences on bone size (e.g., maternal fracture history) and bone turnover, lifestyle issues (e.g., exercise), height loss, weight changes, and other factors. These risk factors have been proven to be important in identifying fracture risk. For example, patients whose BMD was in the lowest third of the study population had about 4.6 times the risk of suffering a hip fracture risk as did women whose BMD was in the highest third. However, hip fracture risk was 17 times greater among the 15 percent of the women who had five or more risk factors (exclusive of bone density) than the 47 percent of the women with two or fewer risk factors (Cummings et al. 1995) (Figure 8-2).

Black et al. (2001) turned the most prevalent risk factors derived from the SOF study into a questionnaire that can be administered to patients (see Table 8-2). By assigning a point value to each of the answers, a summary FRACTURE score is developed. The usefulness of this questionnaire was tested in a large, prospective European study known as EPIDOS. As shown in Figure 8-3, individuals with a higher FRACTURE score had a much higher risk of suffering a hip fracture. It is important to remember, however, that this and other approaches to measuring the risk of fracture may not work as well in certain populations; some of the predictors of fracture for nursing home residents are different than those living in the community. For example, the risk of falling is especially critical in elderly nursing home residents, most of whom have fragile bones (Girman et al. 2002).

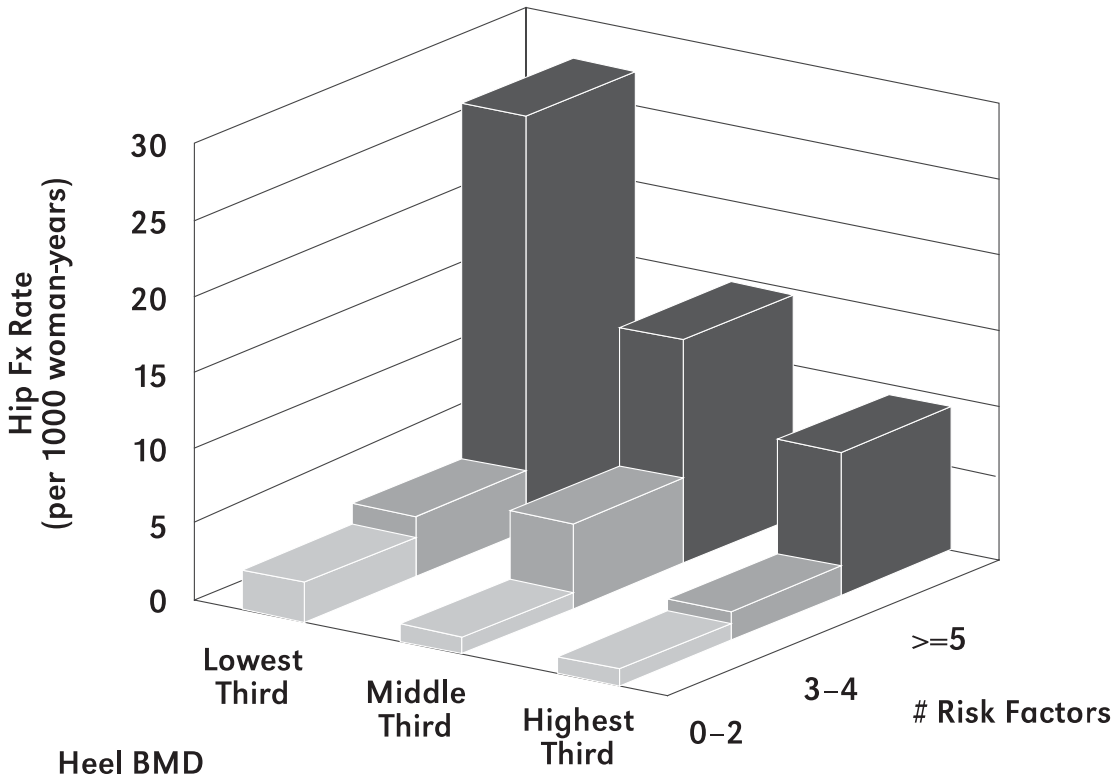
Table 8–1. Risk Factors for Hip Fracture Among Elderly White Women

Variable	Percent Increased Risk
Age (per 5 yr)	40%
History of maternal hip fracture	80%
Height at age 25 (per 6 cm loss)	30%
Previous hyperthyroidism	70%
Current use of long-acting benzodiazepines	60%
Current use of anticonvulsant drugs	100%
Inability to rise from chair	70%
Lowest quartile for depth perception (in vision)	40%
Resting pulse rate greater than 80 beats/min	70%
Any fracture since age of 50	50%

Note: The increases in risk for fracture listed here are from the Study of Osteoporotic Fractures and are all significant. The numbers indicate how much greater the chance of having a fracture is likely to be when these factors are present. Other risk factors have been identified in subsequent studies, for example, weight loss increases the risk of fracture in the elderly (Ensrud et al. 2003).

Source: Based on Cummings et al. 1995.

Figure 8–2. Clinical Risk Factors Independently Predict Hip Fracture Risk



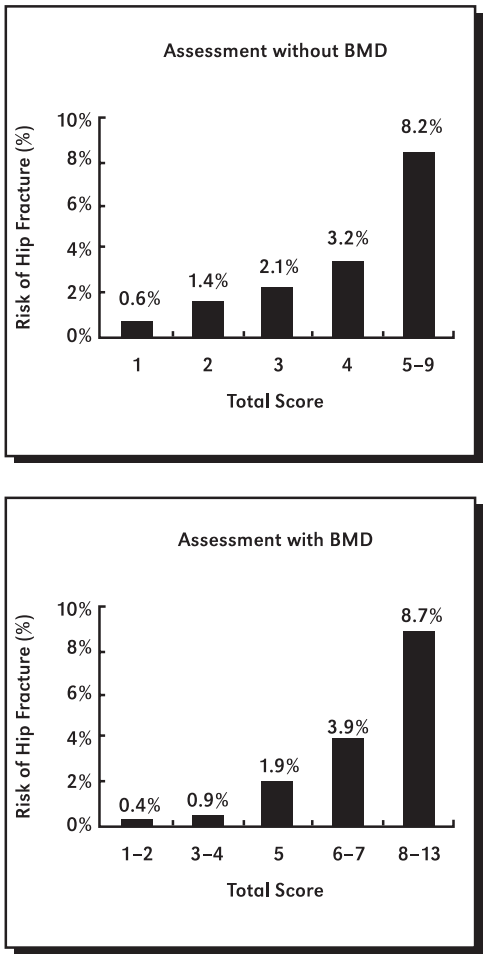
Source: Cummings et al. 1995.

One of the most important needs going forward with respect to risk assessment tools is to incorporate the risk of falling into the system, since so many fragility-related fractures occur as a direct result of a fall. Risk factors for falling include visual or cognitive impairment, use of specific medications, and gait and balance disorders. Poor vision is a particularly important risk factor for the elderly (even those with glasses), since many elderly individuals do not have their eyes and glasses checked regularly. Although high-technology testing of gait and balance are available, these have not been found to be clinically useful as a way to assess the risk of falling. Rather, clinicians rely on patient reports (e.g., prior falls [Nevitt et al. 1991], fear of falling [Tinetti et al. 1994]) and objective examination (e.g., Performance-Oriented Mobility Assessment [Tinetti 1986], Functional Reach [Duncan et al. 1992]). It is important to remember that while any fall should be investigated carefully, those falls

Table 8–2. FRACTURE Index Questions and Scoring

	Point Value
1. What is your current age?	
Less than 65	0
65–69	1
70–74	2
75–79	3
80–84	4
85 or older	5
2. Have you broken any bones after age 50?	
Yes	1
No/Don't know	0
3. Has your mother had a hip fracture after age 50?	
Yes	1
No/Don't know	0
4. Do you weigh 125 pounds or less?	
Yes	1
No	0
5. Are you currently a smoker?	
Yes	1
No	0
6. Do you usually need to use your arms to assist yourself in standing up from a chair?	
Yes	2
No/Don't know	0
If you have a current bone density (BMD) assessment, then answer the next question.	
7. BMD results: Total Hip T-score	
T–score >-1	0
T–score between –1 and –2	2
T–score between –2 and –2.5	3
T–score <-2.5	4

Figure 8–3. Five-Year Risk of Hip Fracture by Quintiles of FRACTURE Index



Note: This FRACTURE Index scoring system places a quantitative value on an individual's risk of fracture; the higher the score, the greater the fracture risk. It was developed from the data of 9704 U.S. white women in the Study of Osteoporotic Fractures and then tested against the EPIDOS database of 7575 French women. As shown in Figure 8-4, the index was predictive of fracture even without BMD, although adding BMD improved the discrimination to some extent. When applied to the EPIDOS data, the discrimination was even greater, for example, the five year fracture risk went from 0.6% for scores of 2–5 to 14.1% for scores of 11-14.

Source: Black et al. 2001.

that lead to fractures are the biggest concern. Individuals who have sustained a fracture as a result of minimal trauma likely do not need further evaluation by BMD testing to be considered in the high-risk category for bone disease and future fractures.

Those individuals who are identified as being both at risk of bone disease and at high risk of a fall might become candidates for further intervention, including exercise programs to improve strength and balance, modifications to the home environment, changes in medications that might make one prone to fall, and use of hip protectors to "cushion the blow" from a fall. (See Chapter 9 for more on hip protectors.)

Step 2: Measuring Bone Mineral Density (BMD) for Individuals at Risk of Osteoporosis

Once a high-risk patient is identified (step 1), further evaluation of that patient is warranted. This section deals with this evaluation process for those at risk of osteoporosis—the most common bone disease.

Why Measure BMD?

BMD testing remains the "gold standard" test for those at risk of osteoporosis. The reason for this is relatively straightforward—in the laboratory, bone strength is strongly related to BMD. More importantly, BMD remains a strong independent predictor of fracture risk. In fact, there is a clear relationship between BMD and fracture risk in older women. For each standard deviation decrease in BMD (in the spine, a one-standard deviation drop represents a loss of 10–12 percent of BMD), the risk of fracture increases by 1.5–2.5 times. The relationship between BMD and fracture is stronger than the relationship between cholesterol and heart attack, and as strong as the relationship between blood pressure and stroke (Marshall et al. 1996). BMD measurement can be used to assess fracture risk and to establish the diagnosis and severity of osteoporosis. BMD testing can be used to assess changes over time (monitoring) in treated and untreated individuals. (It is important to note that while standard x-rays are used to diagnose fractures, they are not useful for measuring bone mass. It is estimated that one must lose 30 percent of BMD for bone loss to be noted on x-ray; furthermore, an improperly performed x-ray in a normal person may have the appearance of bone loss.)

Who Should Have a Bone Density Test and When

As noted earlier, an analysis of risk factors can be helpful in determining who should or should not get a BMD. Risk factors for bone disease and fractures are still not fully understood, especially for younger individuals, males, and non-Whites. In an effort to summarize general conclusions about what is and is not known, a variety of organizations, including government agencies and professional societies, have made attempts to develop guidelines on who should have a bone density test and when. This section reviews those recommendations.

Recommendations for Osteoporosis Screening and for Other Bone Diseases

There is general consensus that all women age 65 and older should have a BMD test, and that women at-risk of bone disease who are under age 65 should also be screened (although there is not universal agreement on what defines "at-risk" status). At present there are no differences in these recommendations across racial and ethnic groups. The U.S. Preventive Services Task Force (USPSTF) recommends bone density screening for all women age 65 and older and for younger postmenopausal women age 60–64 who are at high risk (body weight less than

70 kilograms, no current use of estrogen) (U.S. Preventive Services Task Force 2002). Risk factors that should also be considered include smoking, weight loss, family history, decreased physical activity, alcohol or caffeine use, or low calcium and vitamin D intake. The NOF also recommends testing women age 65 and older, and emphasizes four common and easily assessable risk factors that would justify screening in younger postmenopausal women:

- a family history of osteoporosis;
- a personal history of low-trauma fracture after age 45;
- current cigarette smoking; and
- low body weight (under 127 pounds) (NOF 2003).

The NOF also recommends BMD testing for men who present with fractures or are receiving treatment with a GNRH agonist for prostate cancer, as well as for all individuals who have primary hyperparathyroidism or are on long-term glucocorticoid treatment (National Osteoporosis Foundation 2002). The ISCD agrees with screening all women age 65 and older and also recommends screening healthy men starting at age 70, with earlier testing for men who are at high risk of osteoporosis or fracture (Binkley et al. 2002).

BMD testing should also be performed on any individual who has other potential risk factors for osteoporosis, especially anyone who has had a low-trauma fracture or who exhibit another clinical indication of osteoporosis (e.g., x-ray evidence of low bone mass), as well as those who have diseases or conditions known to cause increased bone loss (e.g., hyperthyroidism [increased activity of the thyroid gland in the neck], hyperparathyroidism [increased activity of the parathyroid gland in the neck], rheumatoid arthritis, certain diseases of the stomach or intestines, long-term menstrual irregularities, cessation of menstrual bleeding) and those who are using a medication that may cause increased bone loss (e.g., glucocorticoids, excessive doses of thyroid hormone, certain blood thinners, certain drugs that treat seizures, drugs that block sex hormone production) (Leib et al. 2004).

Who Should Have a BMD Test?

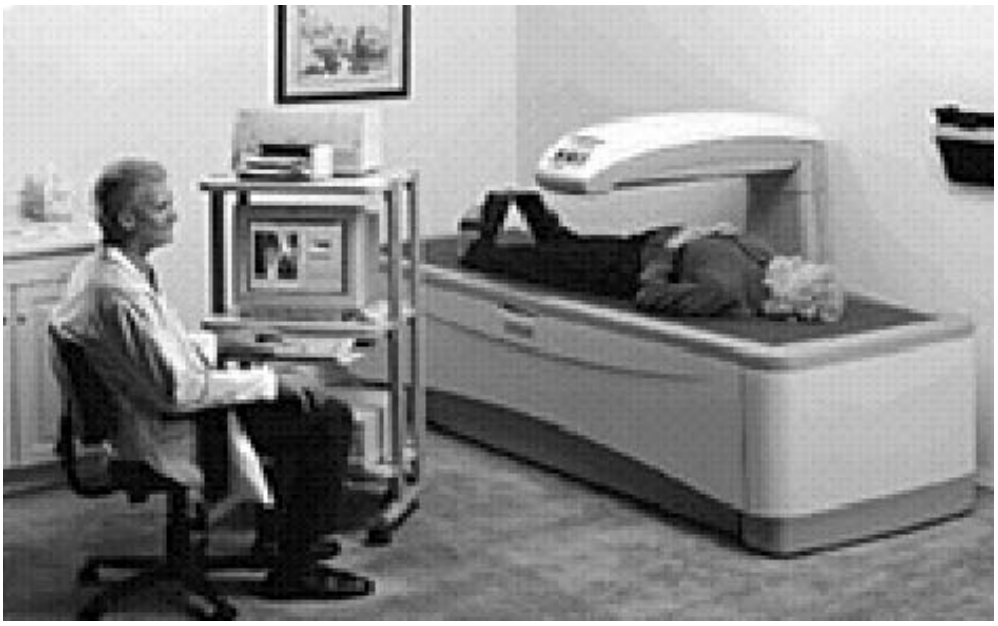
- U.S. Preventive Services Task Force Guidelines
  - ~ All women age 65 and older
  - ~ Women between age 60–64 who are at high risk (body weight less than 70 kilograms, no current hormone therapy)
- National Osteoporosis Foundation Guidelines
  - ~ All women age 65 and older
  - ~ Postmenopausal women under age 65 with:
  - ~ Family history of osteoporosis
  - ~ Personal history of low-trauma fracture after age 45
  - ~ Current cigarette smoking
  - ~ Low body weight (less than 127 pounds)
- Other Clinical Recommendations
  - ~ Low-trauma fractures as an adult
  - ~ Hyperthyroidism
  - ~ Hyperparathyroidism
  - ~ Vitamin D deficiency (osteomalacia)
  - ~ Rheumatoid arthritis
  - ~ Medications that cause bone loss (glucocorticoids, excessive doses of thyroid hormone, medications used to treat seizures, medications that block sex hormone production)
  - ~ Diseases that cause poor intestinal absorption

Methods for Measuring BMD

The most widely accepted method for measuring BMD is dual x-ray absorptiometry (DXA). DXA is very safe, as it involves levels of radiation that are lower than that derived from daily background radiation from the sky when taking a trans-Atlantic airplane flight, and much lower than those from undergoing an x-ray of the back. DXA measures BMD in the spine and hip, sites that are likely to fracture in patients who have osteoporosis (see Figures 8-4 and 8-5). These central skeletal sites are also most appropriate for monitoring the effectiveness of therapy, as they are more likely than peripheral sites to show an increase in BMD in response to treatment. DXA is precise and permits monitoring of patients over time. DXA also can be used to measure bone density in the forearm and whole body.

Several other techniques are available for bone mass measurement and are described briefly below (Genant et al. 1996, Grampp et al. 1997) (Table 8-3). While these methods do assess bone density and may provide an indication of fracture risk, it is important to note that the WHO recommendations and other guidelines for using BMD and interpreting BMD results for diagnosis (see next section for more details)

Figure 8–4. Bone Mineral Density (BMD) Measurements at Spine and Hip

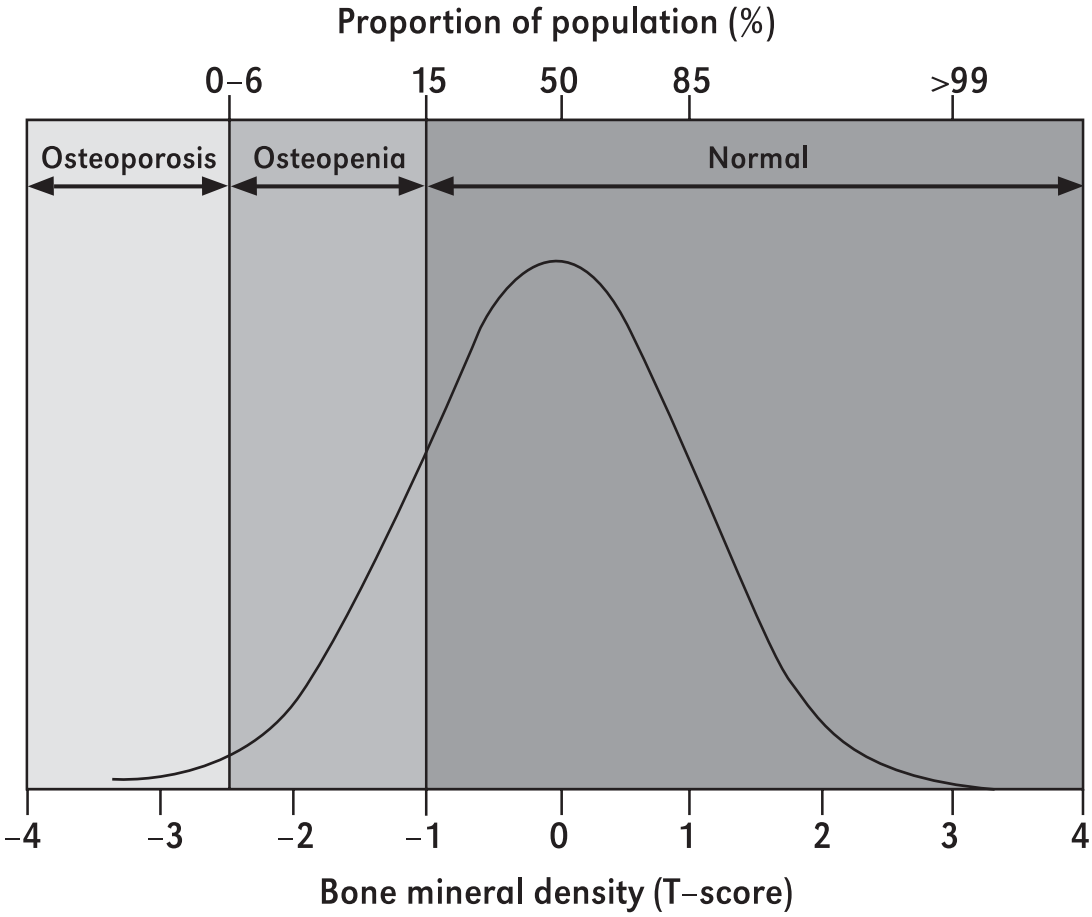


Source: Black 2002.

are based on DXA measurements of the hip or spine. In the future, these alternative tests may be further refined and others may be developed, thus improving the ability to identify individuals at risk of osteoporosis.

- Peripheral DXA (pDXA) uses scaled-down DXA instrumentation to measure peripheral sites such as the forearm, heel, or finger. These tests can help to identify at-risk individuals who are most likely to benefit from further BMD testing. Using the test for this purpose is tricky, requiring the setting of a proper threshold for determining who needs further evaluation. A too-low threshold could prove ineffective in screening, with the result being that many healthy individuals undergo further (expensive)

Figure 8–5. Distribution of Bone Mineral Density in Healthy Women Aged 30–40 Years



Source: Kanis 2002b.

evaluation. A too-high threshold could result in at-risk individuals being "screened out" and thus failing to receive further evaluation that could have resulted in timely diagnosis and treatment of bone disease. At present there is no scoring system for peripheral DXA that has been found to be preferable to using risk factor analysis as a means of determining who should and should not undergo DXA of the spine and hip.

- Peripheral quantitative computed tomography (pQCT) uses specialized equipment to measure cortical bone (the outer, more solid shell of bone) and cancellous bone (the inner, honeycomb-like bone) in the forearm. This technique is used primarily for research.
- Quantitative computed tomography (QCT) uses standard computed tomography equipment, usually with a phantom that must be scanned with the patient. It provides a true volumetric measurement of cancellous bone density in the spine. Although it involves greater radiation exposure, it may be used as an alternative to spine and hip DXA measurements.
- Quantitative ultrasound (QUS) uses sound waves to assess bone mass and thus does not use radiation. It can be used to measure bone in a variety of peripheral sites, such as the heel, tibia (leg), radius (wrist), and finger. Ultrasound devices measure the speed of sound (SOS), as well as specific changes in sound waves (i.e., broadband attenuation or BUA) as the sound waves pass through bone. Most devices use a formula to calculate a bone density equivalent or "T-score equivalent."
- Radiogrammetry uses measurements derived from standard x-rays of the hand to determine an index that compares cortical thickness with the total bone width in the mid-shaft of at least two metacarpal (palm) bones.
- Radiographic absorptiometry (RA), also called photodensitometry, uses a standard x-ray of the hand to measure density in the middle bones of the second, third, and fourth fingers. Specialized equipment is used to scan the film at high resolution, and special software is used to calculate bone volume and bone density. The cortical thickness of the bones also can be measured.
- Single x-ray absorptiometry (SXA) is used to measure peripheral sites such as the heel and forearm. The body part being measured is immersed in a water bath or water equivalent device. The SXA picture is similar to that obtained with DXA technology.

Incorporating these techniques for bone assessment into future clinical trials and observational studies will help in better understanding their appropriate use as a means of predicting the risk of bone disease and fracture.

Using and Interpreting BMD Measurements

BMD in young healthy adults is normally distributed as shown in Figure 8-5. An individual's BMD can be compared to the mean value in a reference population, such as young healthy adults. The difference between an individual's BMD and the mean BMD for the reference population can be expressed in standard deviation (SD) units; a score of 0 indicates BMD equal to the mean; a score of +1 indicates one standard deviation above the mean,

Table 8–3. Techniques for Bone Mass Measurement

Technique	Skeletal sites that can be measured	Time to measure	Radiation exposure (μSv)
DXA	Lumbar spine (PA view) Lumbar spine (lateral view) Proximal femur (hip) Forearm Total body	5–10 minutes	1–7
pDXA	Forearm, heel	<5 minutes	<1
pQCT	Forearm	< 5 minutes	<1
QCT	Lumbar spine	5–10 minutes	50–60
QUS	Heel, forearm, finger, tibia	< 5 minutes	none
Radiogrammetry	Finger	< 5 minutes	< 1
RA	Finger	< 5 minutes	< 1
SXA	Forearm, heel	< 5 minutes	1

Abbreviations: μSv, microsieverts; DXA, dual x ray absorptiometry; pDXA, peripheral dual x ray absorptiometry; pQCT, peripheral quantitative computed tomography; QCT, quantitative computed tomography; QUS, quantitative ultrasound; RA, radiographic absorptiometry; SXA, single x ray absorptiometry.

and a score of -1 is one standard deviation below. When an individual's BMD is compared to the mean BMD score in a young healthy population, this standard deviation measurement is referred to as a T-score. The T-score is calculated using the following formula:

T-Score

$$\frac{\text{Patient's BMD} - \text{Young Normal Mean}}{\text{Standard Deviation of Young Normal Mean}}$$

In 1994, a working group of the World Health Organization developed a classification system for osteoporosis based on BMD using the known gradient of the risk of fracture in the population as a whole. They sought to define osteoporosis using BMD so that the proportion of individuals identified as having osteoporosis by this method would be related to the lifetime risk of fracture in the population. Four general diagnostic categories were proposed for assessments done with DXA (Kanis 1994, Kanis 2002b):

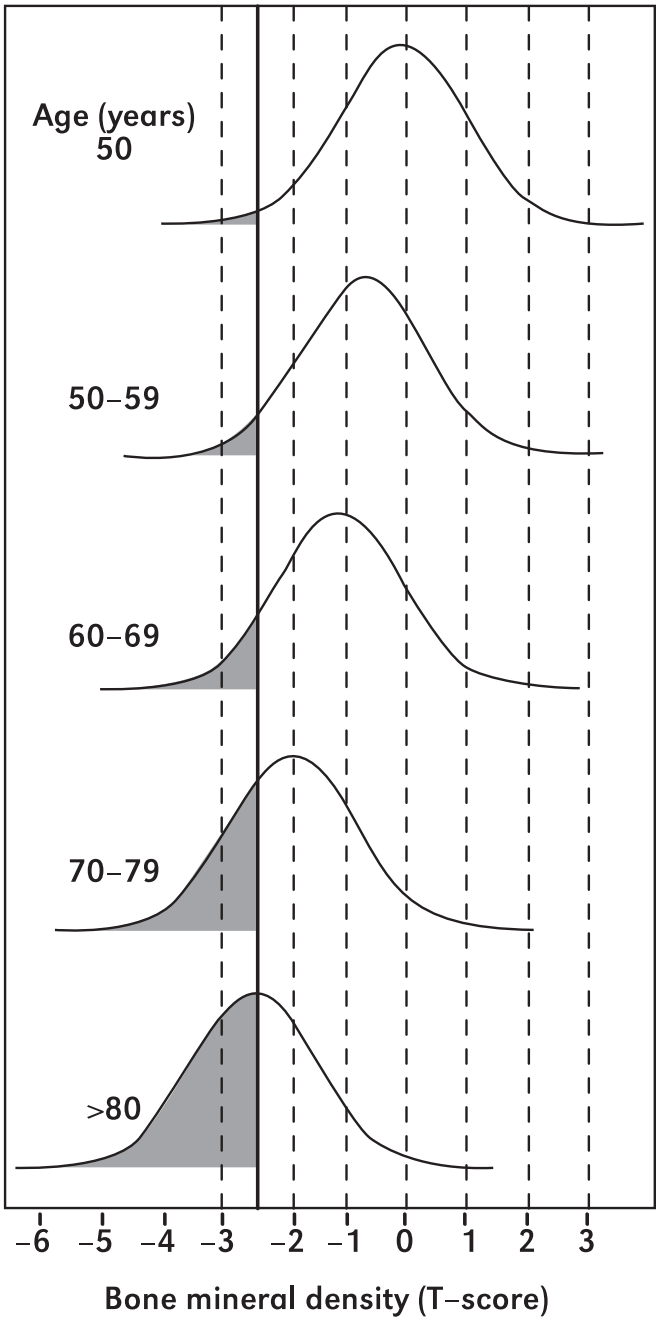
- Normal: Hip BMD that is no more than 1 standard deviation below the young adult female reference mean (T-score greater than -1).
- Low bone mass (osteopenia): Hip BMD that is between 1–2.5 standard deviations below the young adult female mean (T-score less than -1 and greater than -2.5).
- Osteoporosis: Hip BMD that is 2.5 standard deviations or more below the young adult female mean (T-score less than -2.5).
- Severe osteoporosis (established osteoporosis): Hip BMD that is 2.5 standard deviations or more below the young adult mean in the presence of one or more fragility fractures.

In the young healthy population shown in Figure 8-5, about 15 percent of the women have a T-score of less than -1 and thus have low bone mass or osteopenia, while about 0.5 percent of women fall into the osteoporotic range, with a T-score of -2.5 or less. The proportion of women affected by osteoporosis increases with age as average bone density declines (Figure 8-6) and risk of fracture increases.

If there were only a single device for measuring BMD, and only a single skeletal site that was measured, absolute BMD, in g/cm2, could be used. However, it is difficult for clinicians to remember ideal or threshold cut-off points for absolute BMD levels as measured by a single type of machine at various locations, including the spine and hip, let alone remember the values for different types of machines that are calibrated (standardized) differently. The T-score provides a way to use a single set of numbers for all devices and all skeletal sites.

Another way of expressing BMD is the Z-score, which compares an individual with age-, gender-, and ethnicity-matched norms. Z-scores are not used for diagnosis because a person's Z-score can remain constant throughout life, even as BMD declines with age. However, the Z-score is useful in determining how an individual's BMD compares with what is expected for a person of a given age and body size. Although all patients with osteoporosis deserve at least a limited evaluation for secondary causes (i.e., not age-related) of bone loss, patients with a low Z-score (i.e., BMD significantly lower than expected for age and size) are particularly in need of an in-depth evaluation for secondary causes of osteoporosis. Z-scores are also useful in children to determine how their bone density compares to that of their peers. Since they have not reached adult peak bone mass, T-scores should not be used for children. Figure 8-7 is a graphical illustration of T-scores and Z-scores.

Figure 8–6. Distribution of Bone Mineral Density in Women of Different Ages, and the Prevalence of Osteoporosis (Shaded Area). T–score Below –2.5 = Osteoporosis



Source: Kanis 2002b.

The WHO classification was derived from studies of White postmenopausal women and applies to them, but not for men, premenopausal women, or non-White postmenopausal women. In general, men have a higher bone mass than do women of the same age, and Black men and women have higher bone mass do White men and women of the same age (Finkelstein et al. 2002, Looker 2002). Although controversial, the International Society for Clinical Densitometry (ISCD) recommends use of a single normative database (i.e., not adjusted for ethnicity) to calculate T-scores in non-White as well as White postmenopausal women, and use of a male normative database to calculate T-scores for men (Binkley et al. 2002). There are no official recommendations for the BMD standard deviation values that should be used to diagnose osteoporosis in men, premenopausal women, or children. The ISCD emphasizes that the diagnosis of osteoporosis in men, premenopausal women, and children should not be made on the basis of BMD alone (Leib et al. 2004). In fact, a Canadian panel of ISCD has developed guidelines for the diagnosis of osteoporosis in premenopausal women, men, and children (Kahn et al. 2004). This panel recommended that BMD measurements be used only in patients with fragility fractures or major secondary causes of bone loss. The panel also recommended that Z-scores, not T-scores, be used in children and pre-menopausal women. Finally, the panel recommended that the terms osteopenia and osteoporosis not be used for children, since the WHO criteria do not apply to them.

Not everyone with low BMD has osteoporosis; osteomalacia and other bone disorders should also be considered. In addition, as noted previously, low bone density is not the only risk factor for fracture; other factors include age, risk of falling, risk of injury, previous low-trauma fracture, family history of osteoporosis, etc. (see section on Risk Factor Analysis).

The National Osteoporosis Foundation (NOF) and the ISCD recommend using DXA to measure BMD in both the hip and spine and classifying the patient based on the lowest T-score of these measurements (Hamdy et al. 2002, NOF 2003). ISCD recommends using the mean score for the L-1 to L-4 vertebrae to calculate spine BMD and that vertebrae affected by local structural artifacts be excluded from this calculation (Leib et al. 2004). The U.S. Preventive Services Task Force and the Agency for Healthcare Research and Quality (Nelson et al. 2002) state that BMD at the femoral neck is the best predictor of hip fracture and is comparable to spine or forearm BMD for predicting fractures at other sites. ISCD recommends using forearm BMD for obese patients in whom the spine and hip measurements cannot be obtained (Leib et al. 2004).

Finally, when interpreting scores, it is important to remember that DXA measures areal density by calculating grams per square centimeter (bone mineral content divided by area), in contrast to "true" measures of density, which involve volumetric measurement). As a result, DXA underestimates the density of small bones and overestimates the density of large bones. Therefore, the size of the bone should be taken into account when deciding whether or not to medicate.

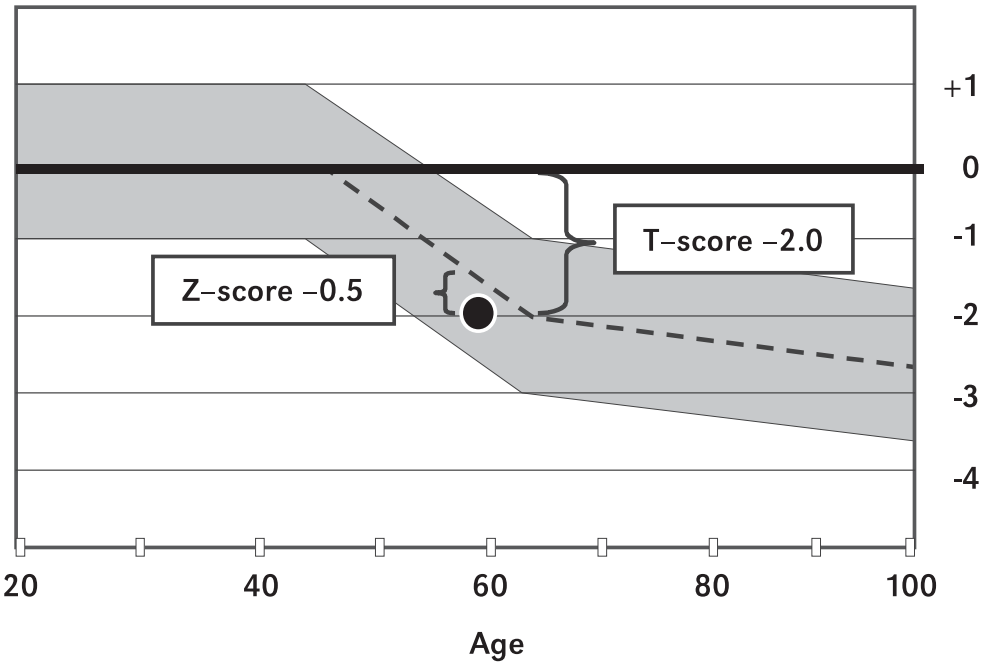
Use of DXA for Monitoring

DXA cannot only be used for making an initial diagnosis and treatment decision, but central DXA is also precise enough to be used for monitoring patients over time, provided the interval between measurements is tailored to the specific patient's situation (Lenchik et al. 2002). More research is needed on the best regimens for follow-up testing and for the best way to interpret changes in BMD in these follow-up

tests. This section reports on the most appropriate approaches, given the current state of scientific evidence.

For individuals who are not currently receiving treatment, the timing of a repeat test should be based on the current BMD and the expected rate of bone loss (e.g., bone loss is faster during early menopause). For older individuals with above-average T-scores, repeat testing may not be necessary at all. For younger individuals who were initially screened due to risk factors but who have normal BMD values, repeating a test every 5–10 years may be helpful. For those with borderline low BMD and/or who may lose bone fairly rapidly (e.g., exposure to high doses of glucocorticoids), repeating the test in 2-3 years would be appropriate. For monitoring patients on treatment (which is the main reason for ongoing monitoring via BMD measurement), testing annually is inappropriate, and there is insufficient evidence to determine if testing every 2 years is useful (Nelson et al. 2002). Nonetheless, many practitioners repeat the test every 2 years for patients on treatment (Medicare covers testing every 2 years), while others wait longer. It is unlikely that repeated BMD

Figure 8–7. T–Scores and Z–Scores



Note: The patient's BMD is represented by a circle, the young normal mean by the bold horizontal line, each 1 SD difference by the lighter horizontal lines, the age-matched mean by the dashed line, and 1 SD above or below the age-matched mean by the shaded area. This 60-year-old woman is 2 SD below the young normal mean (T-score –2.0) and 0.5 SD below the mean for her age (Z–score –0.5).

Source: ISCD 2003.

measurements make a difference in patient compliance with treatment, as many patients who discontinue treatment do so after less than a year (before BMD would be repeated). One exception to the rules related to frequency of testing applies to patients receiving high-dose long-term glucocorticoid therapy, for whom monitoring is recommended every 6 months until BMD is shown to be stable or improved. When repeating BMD measurements, it is important to avoid over-interpretation of small changes as these can be due to differences in equipment or changes in positioning. Non-DXA techniques measuring peripheral sites, QCT, lateral spine DXA, and Ward's triangle DXA (the area of the hip with the lowest density) should not be used for monitoring osteoporosis.

Limitations of BMD Testing

As noted in various sections of this chapter, there are still a number of limitations with respect to BMD testing. Better guidelines are needed on which individuals should receive the test, how to interpret the results of initial and follow-up testing, and how to communicate those results to patients. Health care providers need clear, evidence-based approaches that will enable them to decide who should have BMD testing. They also need guidance in developing plans for treatment and prevention based on a combination of BMD data and other risk factors. More data on the outcomes of screening, prevention, and treatment programs should help to close the large current gap between evidence and practice (Bates et al. 2002, Cummings et al. 2002).

One important concern about the interpretation of results is the variability that exists across different types of BMD machines (even those made by the same manufacturer), and across similar types of machines made by different manufacturers. BMD measured on one type of machine cannot be accurately compared to BMD measured on a different type of machine, nor can BMD performed on the same type of machine at two different locations. There is also variability in the ability of technologists to perform the tests, in the training and ongoing certification of technologists, and in interpretations of results by physicians, each of which can undermine the comparability of results. As a result of all of these factors, daily equipment checks and a quality control system related to both the methodology and reporting of test results is critical to ensure the validity of DXA analysis. The ISCD has developed specific, detailed instructions for quality control as well as reporting of DXA measurements (Leib et al. 2004).

Depending on the skeletal site assessed, the prevalence of osteoporosis can be overestimated (e.g., by use of lateral spine DXA or spinal QCT) or underestimated (e.g., by heel ultrasound) compared to DXA of the spine or hip (Faulkner et al. 1999). There may be differences between the density of skeletal sites within an individual patient. For example, a patient may have a normal spine, but very low bone density at the hip, examination of multiple sites is more likely to result in a diagnosis of osteoporosis. It is important to remember that, despite these limitations, bone mineral density remains the single best predictor of fracture risk available today.

Looking to the Future: Potential Complements to BMD

Researchers in bone disease are developing new approaches that might one day serve as a standard complement to BMD tests. These approaches seek to incorporate additional information that can prove useful in identifying at-risk individuals who may be candidates for further evaluation and treatment, and/or in monitoring the effectiveness of therapy in

patients already being treated. This section reviews these efforts.

Biochemical Markers of Bone Turnover

One major thrust relates to efforts to identify "markers" that reflect the rates at which bone breaks down and builds up. As noted in Chapter 2, bone is continuously remodeled in a process referred to as bone turnover whereby old bone is removed and replaced by new bone. Thus, bone resorption (the breaking down of bone) and formation (the building up of bone) are occurring throughout the skeleton at different sites and at different rates. Tests are now available that look for specific blood and urine markers that reflect the rate of each of these processes for the whole skeleton. While BMD measurements provide valuable information on fracture risk, they contribute no insight into the rate of bone turnover in a given patient. To the extent that the imbalance in the rate of bone resorption and formation may predict the rate of bone loss or enhance the ability to predict the risk of fracture, biochemical markers of bone turnover have the potential to complement the information provided by BMD measurements. As reviewed below, while current bone turnover markers have clear limitations, they do nonetheless have some role today in the management of the patient with osteoporosis, particularly to assess responses to therapy (Looker et al. 2000). With further refinement they are likely to play a more important role in the future.

Table 8-4 lists currently bone turnover markers that are currently available. These can be broadly separated into markers of bone resorption and formation; each of these markers is discussed briefly below.

Resorption Markers. Resorption markers are primarily based on measurement of collagen breakdown products that are released into the circulation as bone is resorbed. In recent years rapid and relatively inexpensive tests capable of measuring these breakdown products have been developed, representing a major advance in this area. Most commonly used are the tests for urine and, more recently, blood (serum) (Looker et al. 2000, Garnero et al. 1998, Miller et al. 1999). These markers measure cross-linked (connected) fragments of type I collagen that are released as bone collagen is broken down (Robins et al. 1994). While initially a sophisticated technique was re-

Table 8–4. Currently Available Bone Biochemical Markers

Resorption markers	Formation markers
N-telopeptide of type I collagen (NTX)	Osteocalcin
C-telopeptide of type I collagen (CTx)	Bone specific alkaline phosphatase (BSAP)
Free and total pyridinolines (Pyd)	Aminoterminal propeptide of type I collagen (PINP)
Free and total deoxypyridinolines (Dpd)	Carboxyterminal propeptide of type I collagen (PICP)

quired to measure these molecules, there are now a number of relatively easy to perform tests that can measure them in the blood and urine (Robins et al. 1995).

Formation Markers: Since bone resorption and formation are coupled processes, blood-based bone formation markers are also useful in assessing bone turnover. Osteocalcin and bone specific alkaline phosphatase (BSAP) can serve as such markers, as they are proteins that are made during the process of bone formation (Deftos et al. 1992, Garnero and Delmas 1993). In addition, since a major product of osteoblasts is type I collagen, tests have also been developed that can measure fragments of the collagen precursor chain that are removed and released into the circulation during the processing of the collagen precursor molecule in bone.

Extensive research studies of bone biochemical markers have uncovered potential clinical uses for these markers. These uses, along with current limitations, are reviewed briefly below.

Estimation of Bone Mass. Bone biochemical markers cannot and should not be used to diagnose osteoporosis or to estimate bone mass; direct measurement of BMD is most effective for these tasks.

Estimation of Fracture Risk. There is evidence to suggest that increased bone turnover may be an independent predictor of fracture risk. In a prospective study of elderly (those over age 75) French women, excess excretion of urinary C–terminal collagen crosslinked peptides (CTx) and free deoxypyridinoline crosslinks (Dpd), two of the commonly used biochemical markers of resorption, was associated with an increased risk of hip fracture, even after adjusting for femoral neck BMD (Garnero et al. 1996). Moreover, in a meta-analysis (combination analysis of multiple studies) of trials using antiresorptive drugs (drugs that slow the breakdown of bone), investigators showed that the change in resorption markers brought on by these agents was related to the reduction in non-spine fracture risk (Hochberg et al. 2002). Specifically, they found that, on average, a drug that reduced bone resorption by 70 percent would decrease the risk of non-spine fractures by 40 percent, independent of effects on BMD. However, while estimation of fracture risk independently of BMD remains an intriguing and potentially important use of bone turnover markers, their routine use for this purpose in individual patients cannot be recommended at this time, largely due to the variability of the measurements.

Estimation of Rate of Bone Loss. Several studies indicate that, at least for groups of individuals, bone biochemical markers can be used to estimate the rate of bone loss. For example, a 4-year study by Garnero et al. (Garnero et al. 1999) found that women with normal bone turnover lost less than 1 percent BMD over 4 years, while those in the high turnover group lost 3–5 times that amount of bone. Here again, the variability of measurements is such that markers may not provide an accurate estimate of bone loss in an individual patient (Nelson et al. 2002).

Selection of Individuals for Therapy. There are reports indicating that individuals with the highest levels of bone turnover appear to have the best response to antiresorptive therapy. In a two-year study of estrogen/progestin treatment, Chesnut and colleagues found that individuals in the highest quartiles for initial excretion of urinary NTx (a biochemical marker) had the greatest gain in BMD in response to hormone treatment (Chesnut et al. 1997). However, the review by the Agency for Healthcare Research and Quality (AHRQ) concluded that studies relating marker results and bone loss had no obvious trend and markers were not useful for patient selection (Nelson et al. 2002). Further studies are needed to evaluate these issues,

particularly with respect to more accurate measurements and better quality control.

Monitoring Effectiveness of Therapy. Perhaps the most important use for bone markers today is in monitoring the effectiveness of ongoing therapy. A number of studies indicate that a significant reduction in bone resorption markers occurs within four to 6 weeks after initiation of antiresorptive therapy, followed by a decrease in bone formation markers in 2-3 months (Garnero et al. 1994). Thus, bone turnover markers could theoretically be used to quickly learn when therapy is not working, certainly much more quickly than could a follow-up BMD test 2 years after initiation of therapy. Markers have been used for this purpose for many years for monitoring the response to treatment in Paget's disease. Failure to show the expected reduction in resorption markers could indicate that the patient is not taking the medication in the prescribed manner or that the dose or type of therapy needs to be changed. However, the review by the AHRQ concluded that no marker could accurately determine if an individual would respond to therapy as confirmed by subsequent BMD measurements (Nelson et al. 2002). Work is ongoing to determine the clinical usefulness of following markers in patients being treated with antiresorptive drugs for osteoporosis.

Summary. To summarize, bone biochemical markers may have a potential future role in the identification and management of the patient with osteoporosis. The remodeling rate itself may play a central role in bone fragility rather than just as a marker of bone loss and future declines in bone mass. When the remodeling rate is high, many of the material qualities of bone that contribute to fragility and inability to resist fracture are sub-optimal (Heaney 2003).

Continued improvements in these markers may lead to their use as independent estimators of fracture risk, of rates of bone loss, and perhaps for optimal selection of patients for specific therapies as well as for monitoring of response to these therapies.

Next-Generation Models for Assessment

Advances in understanding of biochemical markers and genetic factors related to bone disease are leading to the potential for more sophisticated tools for assessing the risk of bone disease in individuals. With that goal in mind, an effort to develop a system that estimates a patient's fracture risk over the next 5–10 years is now underway as a joint activity of the International Osteoporosis Foundation and the National Osteoporosis Foundation of the United States (Kanis et al. 2002a and 2000c). Data from most of the world's epidemiology studies are being merged in order to identify consistent risk factors for fracture and to develop a clinical prediction rule that utilizes this information, plus BMD measurements if available, to estimate an individual's personal fracture risk over the next decade of his or her life. In this scheme the risk of all types of osteoporotic-related fractures (not just hip fractures) would be assessed, so that the entire burden of the disease can be recognized. A patient's personal fracture risk could provide a much better basis for individualized treatment decisions. However, it will be important to validate this approach in the community.

Looking ahead, the evolution of risk factor analysis will likely involve the expansion of generally accepted risk factors such as age, gender, race, and fracture history, all of which are well-established as validated estimators. Other potential risk factors are being studied and may play a larger role in the future. The most promising include biochemical markers of bone metabolism and genetic risk factors, which

represents an evolving area of research. Candidate genes include receptors (proteins in a cell or on its surface that bind specific substances such as hormones and are necessary for these substance to act on the cell) such as the vitamin D or estrogen receptor genes, and components of bone itself, such as the collagen gene. In the future, the characterization of gene subtypes and further clarification of the roles that these and many other genes that regulate bone cells play may allow for the development of assessment tools that are able to identify at an early age individuals at high risk of developing osteoporosis later in life. Additional research on biochemical markers, genetic factors, and other clinical risk factors is needed, especially related to groups other than older White women and to the prediction of fracture risk over the very long term.

Key Questions for Future Research

Assessing the risk of bone disease and fracture remains a challenge. Not all of the risk factors have been identified, and the relative importance of those that are known remains unclear. The answers to the following research questions can help in meeting this challenge:

- What strategies would be most effective in promoting the cost-effective use of bone densitometry more broadly to the at-risk population?
- Given the limitations of bone densitometry, what tests and/or tools are most effective in predicting the risk of fracture and/or deformity in an individual? Which tools are most practical in different clinical settings? What existing and yet-to-be-identified risk factors are most effective at predicting this risk?
- What practical methods are most effective at assessing the other part of the definition of osteoporosis—"micro-architectural deterioration" (changes that occur in bone because of deterioration of its fine structure)—especially at high-risk sites such as the vertebral bodies and proximal femur. New imaging techniques will be important not only in analyzing skeletal microarchitecture, but also in detecting early skeletal lesions (e.g., in those who have Paget's disease or cancer).
- How can biochemical markers best be used in assessing fracture risk? One key requirement will be the standardization and quality control of current assays of bone remodeling.
- Are there new, as yet undiscovered biochemical markers of bone resorption and formation that could be useful in assessing fracture risk? Can these markers be identified through detailed studies of proteins produced by bone cells and deposited in bone matrix?

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