Epidemiology, etiology, and diagnosis of osteoporosis

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Epidemiology
Etiology
Diagnosis
Fracture

Osteoporosis, a major public health problem, is becoming increasingly prevalent with the aging of the world population. Osteoporosis is a skeletal disorder characterized by compromised bone strength, which predisposes the individual to an increased risk of fractures of the hip, spine, and other skeletal sites. The clinical consequences and economic burden of this disease call for measures to assess individuals who are at high risk to allow for appropriate intervention. Many risk factors are associated with osteoporotic fracture, including low peak bone mass, hormonal factors, the use of certain drugs (eg, glucocorticoids), cigarette smoking, low physical activity, low intake of calcium and vitamin D, race, small body size, and a personal or a family history of fracture. All of these factors should be taken into account when assessing the risk of fracture and determining whether further treatment is required. Because osteoporotic fracture risk is higher in older women than in older men, all postmenopausal women should be evaluated for signs of osteoporosis during routine physical examinations. Radiologic laboratory assessments of bone mineral density generally should be reserved for patients at highest risk, including all women over the age of 65, younger postmenopausal women with risk factors, and all postmenopausal women with a history of fractures. The evaluation of biochemical markers of bone turnover has been useful in clinical research. However, the predictive factor of these measurements is not defined clearly, and these findings should not be used as a replacement for bone density testing. Together, clinical assessment of osteoporotic risk factors and objective measures of bone mineral density can help to identify patients who will benefit from intervention and, thus, can potentially reduce the morbidity and mortality associated with osteoporosis-associated fractures in this population.

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Epidemiology of osteoporosis

Prevalence

Elderly people are the fastest growing population in the world and, as people age, bone mass declines and the risk of fractures increases. Osteoporosis, defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture, is a major public health problem throughout the world. The social and economic burden of osteoporosis is increasing steadily because of the aging of the world population. Currently affecting more than 10 million people in the United States, osteoporosis is projected to impact approximately 14 million adults over the age of 50 by the year 2020. Worldwide, approximately 200 million women have osteoporosis. Although the likelihood of developing osteoporosis currently is greatest in North America and Europe, it will increase...
in developing countries as population longevity in these countries continues to increase.\(^2\)

**Clinical consequences**

The annual incidence of osteoporotic fractures exceeds 1.5 million in the United States.\(^3\) Hip fractures, long considered more devastating than any other type of osteoporotic fracture, are projected to increase from an estimated 1.7 million in 1990 to 6.3 million by the year 2050.\(^1\) Notably, 1 in 5 persons die during the first year after a hip fracture,\(^5\) whereas nearly one third require nursing home placement after hospital discharge, and fewer than one third regain their prefracture level of physical function.\(^6\) Vertebral fractures also are associated with an increased incidence of morbidity, including back pain, height loss, deformity (kyphosis), disability, and mortality.\(^7,8\)

Moreover, multiple thoracic fractures can result in restrictive lung disease, and altered abdominal anatomy caused by lumbar fractures can lead to constipation, abdominal pain, distention, reduced appetite, and premature satiety. The pain, physical limitations, and lifestyle and cosmetic changes caused by osteoporotic fractures can have serious psychologic effects, including depression, loss of self-esteem, anxiety, fear, anger, and strained interpersonal relationships.\(^9-11\)

**Economic burden**

Osteoporotic fractures cost the US health care system approximately $17 billion annually, with an annual cost projected to approach $50 billion by the year 2040.\(^12,13\) These direct medical costs represent a greater burden than the projected annual costs of stroke, breast cancer, diabetes, or chronic lung disease.\(^13\) Worldwide, the economic burden of osteoporosis parallels that seen in the United States, with expenditures for osteoporotic fractures rising faster than the general rate of inflation in almost every country.\(^1\) Also, the indirect cost of osteoporotic fractures, the costs associated with fracture-related morbidity and mortality, are substantial. Clearly, the clinical and economic consequences of osteoporosis call for a concerted effort to assess patients at risk to allow for prevention and early intervention when appropriate.

**Etiology and pathogenesis of osteoporosis**

Bone strength reflects the integration of 2 main features: bone density and bone quality.\(^5\) Many factors contribute to the risk of osteoporotic fractures, all of which should be taken into account in the assessment of fracture risk in patients (Figure).\(^14\)

**Impact of bone density and bone quality on the risk of fracture**

The World Health Organization (WHO) has defined criteria for assessing bone status and determining the risk of fracture. These criteria are defined by the T-score, which is the number of standard deviations (SDs) by which a patient’s test result exceeds (positive T-score) or falls below (negative T-score) the mean of the young adult group.\(^15\) Bone density—also called bone mineral density (BMD)—is expressed as a relationship to 2 norms: the T-score and the Z-score (the expected BMD for the individual’s age and sex).\(^12\) This criterion of bone density is used conventionally as a proxy for overall bone strength and is expressed as grams of mineral per square centimeter or grams per cubic centimeter.\(^16\) Evidence that the risk of fracture increases as BMD declines has been demonstrated in multiple epidemiologic studies.\(^17-20\) For example, in the European Prospective Osteoporosis Study with a cohort of 1924 women, the risk of incident vertebral fracture increased by a factor of 1.5 per 0.1 g/cm\(^2\) decrease in the spinal BMD value. Although BMD is the standard test for the diagnosis of osteoporosis before treatment, ongoing research indicates that BMD measurement alone may not be adequate for assessing fracture risk and treatment efficacy. A more useful concept may be bone quality, which reflects the integration of both BMD and bone strength. Bone strength is determined by structural and material properties that impact overall bone quality.\(^21,22\) The structural properties of bone include geometry (size and shape) and microarchitecture (eg, trabecular thickness and connectivity and cortical thickness/porosity). The material properties of bone include mineralization (mineral-to-matrix ratio and crystal size), collagen composition (type and cross-links), and damage accumulation (such as microfractures). These components of bone strength are affected by the bone turnover rate, in which old bone is resorbed and new bone is created.\(^21,22\) In older women, abnormalities in the bone remodeling process compromise these properties, increasing the propensity for fracture.\(^23\) In addition, estrogen deficiency after menopause has been associated with an accelerated loss of bone and bone turnover, leading to a substantial increase in the risk for fracture.\(^22,23\) Decreases in estrogen levels increase bone resorption by lengthening the life span of osteoclasts and decrease bone building by shortening the life span of osteoblasts.\(^23\) Antiresorptive agents have been shown to reduce the risk of vertebral fracture without producing large gains in lumbar spine BMD, providing evidence that factors other than BMD play a role in bone strength.\(^24\) In these patients, changes in bone turnover markers may also be evaluated to help assess bone strength and fracture risk reduction.

**Pathogenesis of osteoporosis**

Normal bone turnover involves a balance between the processes of bone resorption and bone formation in which osteoclasts remove (resorb) bone by acidification and proteolytic digestion and osteoblasts secrete osteoid
(organic matrix of bone) into the resorption cavity. In postmenopausal women, the rate of bone turnover increases dramatically and remains elevated for up to 40 years after cessation of ovarian function, leading to continuous, progressive bone loss. The basis for the increased bone turnover is thought to be due in part to a shortening of the lifespan of osteoblasts and a prolongation of the lifespan of osteoclasts.

Risk factors for osteoporosis and osteoporotic fractures

Several interacting factors contribute to the risk of osteoporotic fracture, including clinical, medical, behavioral, nutritional, and genetic variables.

Clinical factors

A major determinant of bone density in an older individual is her or his peak bone mass. Although the attainment of peak bone mass begins in utero and is typically complete by age 40, the main contributor to this process is the amount of bone that is gained during adolescence. Generally, it is thought that low peak bone mass is associated with an increased risk of osteoporotic fracture, although the role of peak bone mass as a factor in osteoporosis has not been thoroughly explored.

In the first years after cessation of ovarian function at menopause, bone loss accelerates and bone mass continues to decline with age. Therefore, in addition to peak bone mass, aging itself is a risk factor for bone loss.

Postmenopausal women with a low body weight, low percentage of body fat, or low body mass index are at increased risk of low bone mass and rapid bone loss, both of which are independent contributing factors to postmenopausal osteoporosis.

In women aged 65 years or older, both low serum total estradiol concentrations (<5 pg/mL) and high serum concentrations of sex hormone-binding globulin (≥1 μg/dL) have been shown to increase the risk of hip and vertebral fractures, without relation to BMD. The strong association between a history of hyperthyroidism and the risk of hip fracture in elderly women, also independent of BMD, may be attributable to long-lasting impairment of bone strength, neuromuscular...
function, and/or muscle strength. Several studies also have documented an association between prior fracture history at any site and the risk of future vertebral and hip fractures. These observations suggest that existing defects in bone microarchitecture may influence the risk of fracture and that this risk may be independent of BMD. Moreover, it has been shown that in women who have an incident vertebral fracture develop, 1 in 5 have a new vertebral fracture develop in the subsequent year. Impaired vision (ie, poor depth perception and reduced ability to perceive contrast) independently increases the risk of hip fracture in elderly white women and contributes to the propensity to fall, which is another independent risk factor for fracture. Poor hand grip strength, which can be caused by cognitive impairment, joint disorders, diabetic neuropathy, and/or pain, is a strong independent risk factor for fragility fractures in postmenopausal women.

Medical factors

Secondary osteoporosis is associated with a number of medical disorders, including gastrointestinal diseases (eg, malabsorption syndromes and inflammatory bowel disease), hematologic disorders (eg, thalassemia and pernicious anemia), and hypogonadal states (eg, amenorrhea). Moreover, exposure to certain medications may contribute to and/or exacerbate osteoporosis (Table I). Glucocorticoids are the most commonly implicated class, affecting both the quantity and quality of bone. The magnitude of the increased risk of vertebral fracture in glucocorticoid-treated men and women is disproportionate to observed decreases in BMD, leading investigators to speculate that in addition to reducing bone mass, glucocorticoid treatment may lead to bone quality defects mediated by increases in bone turnover and trabecular perforation. Postmenopausal women who already have low bone mass are likely to reach a fracture threshold with glucocorticoid treatment sooner than patients with initially higher BMD values.

Behavioral factors

Several behavioral risk factors increase the odds of developing osteoporosis and atraumatic fractures. One is cigarette smoking, which is associated with accelerated bone loss and increased risk of hip fracture in the elderly, apparently caused at least in part by reduced intestinal calcium absorption efficiency. A low level of physical activity has been positively correlated with the risk of fracture in certain studies. After adjustment for confounding variables (eg, self-rated health and neuromuscular function), this correlation did not always remain significant in clinical studies. Alcohol intake of 207 mL or more (≥7 fl oz) per week is a risk factor for bone loss. In addition, caffeine intake has been correlated positively with the risk of hip fracture and the rate of bone loss in elderly women with the tt variant of the vitamin D receptor.

Nutritional factors

Dietary calcium intake is correlated modestly with BMD, although this relationship is apparent mainly in lean men and women with low body mass index values (<27 kg/m²). Vitamin D deficiency is an established risk factor for fractures in the elderly, due to the higher bone turnover, reduced calcium absorption, and loss of bone mass resulting from secondary hyperparathyroidism. A number of prescription medications also have been shown to interfere with calcium absorption, including diuretics, corticosteroids, anticonvulsants, immunosuppressive medications, nonsteroidal anti-inflammatory drugs, asthma medications with corticosteroids, and a number of antibiotics (Table I).

Genetic factors

Race is a key determinant of BMD and the risk of fracture. Incidence rates obtained from studies among different racial and ethnic groups demonstrate that although women have higher fracture rates compared with men overall, these differences vary by race and age. For example, in white and Asian subjects, women had higher rates for all age groups older than 50 years. For Hispanic subjects aged 50 to 59 years, men had a higher rate than women, but this gender relationship reversed after age 60. Black men had higher rates than black women until age 70, after which the women had higher rates. For both genders and all race and ethnic groups, the rates increased sharply with age. Studies conducted in the United States that directly compared non-Hispanic white, Asian, Hispanic, and black subjects have shown that Asian subjects, a population that usually has low bone mass, did not have an increased rate of

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**Table I** Medical therapy that may be associated with reduced bone mass in adults

<table>
<thead>
<tr>
<th>Medication</th>
<th>Lithium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>Heparin (long-term use)</td>
</tr>
<tr>
<td>Anticonvulsants (phenobarbital, phenytoin)</td>
<td>Progesterone (parenteral, long-acting)</td>
</tr>
<tr>
<td>Benzodiazepines (long-acting)</td>
<td>Supraphysiological thyroxine</td>
</tr>
<tr>
<td>Cytotoxic drugs</td>
<td>Tamoxifen (premenopausal use)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Total parenteral nutrition</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone agonists</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from National Osteoporosis Foundation.
hip fractures compared with non-Hispanic black and Hispanic subjects.\textsuperscript{45} The highest mean BMD values and lowest hip fracture rates have been reported for black women.\textsuperscript{5,46} These results demonstrate that race and ethnicity, as well as age and gender, influence the incidence of hip fractures. Nonetheless, in a retrospective review, black patients experienced a longer period of hospitalization after hip fracture and were more likely to be nonambulatory at discharge than white patients.\textsuperscript{47} Moreover, using Health Care Financing Administration data from 1980 to 1982, black women had a higher mortality rate during hospitalization for hip fracture than white women.\textsuperscript{48}

Body size is another factor affecting the risk of fracture. One study in older, non-Hispanic white women showed that older women with smaller body builds are at increased risk of hip fracture because of lower hip BMD values.\textsuperscript{49} Although all measurements of body size (including total body weight, percentage weight change since age 25, lean mass, fat mass, body fat percentage, hip girth, body mass index, and modified body mass index) were associated with hip fracture risk, measurement of total body weight by itself was found to be sufficient for ascertaining hip fracture risk and was not improved by measurements of the other attributes of body size and composition.\textsuperscript{49}

Women with a maternal history of hip fracture are approximately twice as likely to experience hip fractures as women without such a family history.\textsuperscript{32,36}

### Predicting fracture risk in postmenopausal women: The FRACTURE Index

Recently, investigators from the Study of Osteoporotic Fracture Research Group developed the FRACTURE Index, an algorithm to predict the risk of hip, vertebral, and nonvertebral fractures using easily assessed risk factors.\textsuperscript{50} The FRACTURE Index was designed to be used as a tool not only for physicians but for patients. As a self-administered questionnaire, women assess their risk for fracture and use the results to facilitate a discussion with their physicians.\textsuperscript{50} As shown in Table II, this instrument takes into account the major established risk factors, which include age, personal history of fracture, maternal history of hip fracture, weight, smoking status, and mobility.\textsuperscript{50} The maximum possible score is 11 without BMD information and 15 with BMD information, and the investigators recommend that postmenopausal women with a total score 4 or greater without BMD assessment or 6 or greater with BMD assessment should undergo further evaluation by their physician.\textsuperscript{50} Further evaluation may include a thorough physical examination, medical history, and radiographs to ensure no prior fractures. In addition, a comprehensive chemistry profile, tests for thyroid function, serum or urinary calcium level, vitamin D level, and bone turnover markers may help determine or rule out any secondary causes of osteoporosis or underlying metabolic diseases that may affect bone health. However, it should be noted that this scoring system was designed for risk assessment in older, postmenopausal white women and may not be applicable to other population groups.\textsuperscript{50}

### Diagnosis of osteoporosis

Assessment of existing bone mass, determining the fracture risk based on this clinical assessment, and making decisions regarding the appropriate therapeutic intervention are the ultimate goals when evaluating patients for osteoporosis.\textsuperscript{5}

The WHO established diagnostic criteria for osteoporosis on the basis of BMD T-scores.\textsuperscript{15} The T-score describes the patient’s BMD in terms of the number of SDs by which it differs from the mean peak value in young, healthy persons of the same sex.\textsuperscript{51} The WHO uses a threshold of 2.5 SDs below the mean of young adult women as the criterion for a diagnosis of osteoporosis.\textsuperscript{15} The criterion for a diagnosis of osteopenia (low

<table>
<thead>
<tr>
<th>Questions</th>
<th>Point value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is your current age?</td>
<td>0</td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>1</td>
</tr>
<tr>
<td>65-69 y</td>
<td>2</td>
</tr>
<tr>
<td>70-74 y</td>
<td>3</td>
</tr>
<tr>
<td>75-79 y</td>
<td>4</td>
</tr>
<tr>
<td>≥ 85 y</td>
<td>5</td>
</tr>
<tr>
<td>2. Have you broken any bones after age 50?</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No/don’t know</td>
<td>0</td>
</tr>
<tr>
<td>3. Has your mother had a hip fracture after age 50?</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No/don’t know</td>
<td>0</td>
</tr>
<tr>
<td>4. Do you weight 125 lb or less?</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>5. Are you currently a smoker?</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>6. Do you usually need to use your arms to assist yourself in standing up from a chair?</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No/don’t know</td>
<td>0</td>
</tr>
<tr>
<td>7. What was your total hip T-score?</td>
<td>3</td>
</tr>
<tr>
<td>≥ −1.0</td>
<td>0</td>
</tr>
<tr>
<td>Between −1.0 and −2.0</td>
<td>2</td>
</tr>
<tr>
<td>Between −2.0 and −2.5</td>
<td>4</td>
</tr>
</tbody>
</table>

Adapted from Black et al.\textsuperscript{50}
bone mass) is more than 1.0 SD but less than 2.5 SDs below the reference mean. However, T-scores were developed for the estimation of the prevalence of osteoporosis across populations not for the assessment of osteoporosis in specific patients. Moreover, although T-scores originally were based on the BMD of the hip measured by dual-energy x-ray absorptiometry (DXA), the scores are now applied to BMD at other skeletal sites and/or measured by different methods. Currently, the National Osteoporosis Foundation and the International Society for Clinical Densitometry consider central DXA of the hip and/or spine as the preferred measurement for a diagnosis of osteoporosis.

**Candidates for assessment**

The National Osteoporosis Foundation, US Preventative Services Task Force, and the American Association of Clinical Endocrinologists recommend that BMD testing be performed to guide treatment decisions, based on the patient’s risk profile. Specifically, BMD testing is indicated for all women aged 65 years or older irrespective of other risk factors, for younger postmenopausal women with 1 or more risk factors, and for postmenopausal women who have had fractures (to confirm the diagnosis and to determine disease severity).

**Methods of assessment**

**Patient history and physical examination**

Many metabolic bone diseases, such as hyperparathyroidism and osteomalacia, also are associated with low BMD measurements; therefore a complete and thorough history taking and physical examination are essential to establishing a correct diagnosis of osteoporosis. A complete history should be obtained, with specific attention given to the previously discussed risk factors, including medical, family, and medication histories.

Although patients with decreased BMD values usually have no specific abnormal physical findings, a thorough physical examination may detect kyphosis, a protruding abdomen, and height loss, which signify prevalent vertebral compression fractures; back tenderness, which is usually present only after an acute fracture; reduced gait speed or grip strength, which often are reduced in patients who have had or are about to have a hip fracture; and poor visual acuity, which is a risk factor for falling.

Certain other physical findings, such as nodular thyroid, hepatic enlargement, jaundice, or cushingoid features, may reveal secondary causes of osteoporosis (eg, hyperparathyroidism, liver disease, or Cushing’s syndrome). A low Z-score (based on the number of SDs below the BMD of an age-matched population of the same sex) also may be indicative of secondary osteoporosis.

**Radiologic and laboratory assessments**

**Assessments of BMD**

BMD is the standard tool used to diagnose osteoporosis. Several methods of imaging have been developed to measure BMD, including DXA and quantitative computed tomography (QCT). The WHO guidelines for the diagnosis of osteoporosis are based on DXA measurements of the hip or spine.

**DXA**

DXA is considered the gold standard of methods used to diagnose osteoporosis. This test is capable of measuring bone mineral content at any site in the body but usually is used at central sites (the lumbar spine and the proximal femur) and peripheral sites, including the distal forearm. This is accomplished by passing 2 beams of different energies through the bone at the site being measured. A major advantage of DXA is that it exposes the patient to radiation levels approximately 90% less than a standard chest radiograph. The unit of measurement for bone density with the use of DXA is areal density (g/cm²); however, BMD is reported as a T-score on the basis of this measurement.

Peripheral DXA techniques analyze BMD at the distal radius and the calcaneus with high precision and low radiation exposure. Because these measurements are less useful in predicting the risk of fractures of the spine and proximal femur than spinal and hip DXA, a low BMD value obtained by peripheral techniques is not sufficient for a diagnosis or for making treatment decisions, but it does warrant further assessment. In addition, peripheral sites are less likely than central sites to show an increase in BMD in response to treatment.

**QCT**

QCT also can be used to measure BMD of the lumbar spine or peripheral sites. Although BMD can be measured by QCT on any computed tomographic system, the equipment has to be calibrated by using a calibration phantom that contains elements with standardized densities of calcium hydroxyapatite. The accuracy of QCT of the spine in predicting spinal fracture is comparable to that of DXA but has the advantage of measuring true volumetric, or 3-dimensional, BMD, in contrast to the areal BMD obtained from DXA. QCT can distinguish between cortical and trabecular bone and thus is more sensitive to changes in BMD caused by the higher bone turnover rate of trabecular bone. It is also precise enough to detect skeletal changes over time, and it can be used to follow the disease state or to monitor results of osteoporosis therapy.

Although these imaging techniques are useful for determining BMD when diagnosing osteoporosis, the
role of BMD measurement in assessing treatment efficacy, particularly fracture risk reduction, remains unclear.\textsuperscript{59-61} As seen in separate analyses for alendronate, raloxifene, and risedronate, increases in lumbar spine BMD with each therapy explain only a small portion (<20\%) of the vertebral fracture risk reduction observed with these agents. Therefore, increases in BMD seen with treatment are not very predictive of the magnitude of vertebral fracture risk reduction.

Biochemical markers of bone turnover

Biochemical markers of bone turnover have been used widely in clinical research and represent the products of bone formation and resorption that are released into the circulation (Table III).\textsuperscript{62} Quantitative changes in markers reflect the dynamic process of bone metabolism. For example, in postmenopausal women, bone formation and resorption markers are significantly higher than those of premenopausal women, reflecting the high bone turnover rate and associated bone loss that occurs with estrogen deficiency.\textsuperscript{26,62} In contrast, antiresorptive agents, which decrease osteoclastic activity, are associated with a decrease in bone-turnover markers and an increase in bone density in postmenopausal women.\textsuperscript{27,63-67}

Table III  Currently available bone turnover markers

<table>
<thead>
<tr>
<th>Bone-formation markers</th>
<th>Bone-resorption markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>Serum</td>
</tr>
<tr>
<td>Bone-specific alkaline phosphatase</td>
<td>Cross-linked C-telopeptide of type I collagen</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>Tartrate-resistant acid phosphatase</td>
</tr>
<tr>
<td>Carboxyterminal propeptide of type I collagen</td>
<td>N-telopeptide of collagen cross-links</td>
</tr>
<tr>
<td>Aminoterminal propeptide of type I collagen</td>
<td>C-telopeptide of collagen cross-links</td>
</tr>
<tr>
<td></td>
<td>Hydroxyproline</td>
</tr>
<tr>
<td></td>
<td>Pyridinolines</td>
</tr>
<tr>
<td></td>
<td>Deoxypyridinolines</td>
</tr>
<tr>
<td></td>
<td>N-telopeptide of collagen cross-links</td>
</tr>
<tr>
<td></td>
<td>C-telopeptide of collagen cross-links</td>
</tr>
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</table>

Markers of bone-formation are released from osteoblasts and typically are measured in serum.\textsuperscript{62,68} Largely because of their tissue specificity and assay sensitivity, the most useful markers are bone-specific alkaline phosphatase (BSAP) and osteocalcin.\textsuperscript{62,69-71} Although type I collagen is the major product synthesized and secreted by osteoblasts, it also is produced by other tissues and current assays lack selectivity for bone derived type I collagen.\textsuperscript{62} In addition, current assays for quantitating BSAP and osteocalcin are more effective at differentiating between normal and disease states compared with those for type I collagen.\textsuperscript{62}

Bone-resorption markers are secreted during osteoclastic activity and include the collagen breakdown products pyridinoline, deoxypyridinoline, and cross-linked C- and N-telopeptides. Multiple assays are now available that can measure these products relatively quickly and inexpensively.\textsuperscript{62} Tartrate-resistant acid phosphatase, which is a lysosomal enzyme present in cells, until recently was limited as a bone-resorption marker because early assays lacked specificity for the osteoclast-derived enzyme (TRACP) and because of its instability in assay samples.\textsuperscript{62,72} Newer assays are now available that are selective for TRACP 5b, the osteoclast-specific isoform that is considered to be a promising marker for predicting vertebral fractures.\textsuperscript{72-74} Indeed, in large prospective studies, biochemical markers of bone resorption have been associated with increased vertebral and nonvertebral fractures independently of BMD. However, their use in predicting fracture risk in specific patients has not been defined clearly. The value of these markers in the assessment of fracture risk therefore is likely to be in combination with other important risk factors, including BMD.\textsuperscript{62,68}

Other potential uses of turnover markers include the ability to monitor drug efficacy, to predict increases in bone mass, and to assist in the selection of patients for treatment. Bone-turnover markers have little or no use in the diagnosis of osteoporosis, in the prediction of bone mass, and in the ability to monitor compliance.\textsuperscript{62}

Conclusion

The clinical consequences and economic burden of osteoporosis indicate a need for intervention in women at high risk. Many risk factors are associated with osteoporosis and fracture, including low-peak bone mass achieved during growth, hormonal factors, the use of certain drugs, cigarette smoking, low physical activity, low intake of calcium and vitamin D, race, small body size, and a personal or family history of fracture. All these factors should be taken into account when assessing the risk of fracture to determine which patients require further assessment and/or treatment. Although all postmenopausal women should be evaluated by a thorough physical examination and history taking, radiologic laboratory assessments of BMD should be reserved for those patients at highest risk. These include all women over the age of 65, younger postmenopausal women with risk factors, and postmenopausal women with a history of fractures. Although biochemical markers of bone turnover have demonstrated utility in clinical research and trials, use of such testing in specific patients is not defined clearly and is not a replacement for BMD testing. Together, the judicious use of risk
factor assessment and objective measures of bone strength can help to identify patients who would benefit from intervention, thus potentially reducing the social and economic burden of osteoporosis.

Acknowledgment

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